THE JOURNAL

OF

UROLOGY

VOLUME IV

BALTIMORE, MD.
1920

CONTENTS

Number 1, February, 1920

Number 2, April, 1920

Number 3, June, 1920

Number 4, August, 1920

Number 5, October, 1920

Number 6, December, 1920

/

URINARY TRACT PURPURA: A PROBABLE ENTITY[1]

A. RAYMOND STEVENS AND JOHN P. PETERS, JR.

In June, 1918, we published a preliminary report (1) of a group of cases that presented as a distinguishing feature a purpuric condition confined in at least the majority of cases to the urinary tract. The onset was acute; the course marked by temperature of an irregular type, general febrile symptoms, gross hematuria, frequency of urination and dysuria. The work has been continued, more material studied and more methods employed. The complete results of this study are incorporated in this report. Although the etiology of the condition has not been established, we feel that there is sufficient evidence to justify us in assuming that we are dealing with a new disease.

In 1916 Sir John Rose Bradford (2) noted the presence of a distinct hemorrhagic nephritis. His description of this type of case is so perfectly applicable to our own group of cases that we shall quote from it directly:

> In some instances, especially if the case is seen early, the urine may contain a large quantity of blood, so as to be obviously red to the eye. . . . . Such cases present a rather different clinical picture to the general run of cases, in that with them dropsy is neither so frequent, nor when present, so marked a feature of the case. Further, these hemorrhagic cases more frequently have pyrexia and resemble much more closely in their course infective nephritis dependent upon some microbic invasion. . . . . In a few instances the hematuria and pyrexia have been intermittent and recurrent, producing a clinical picture closely resembling that seen in renal embolism; but these patients have not been suffering from any condition liable to cause

[1] The work here reported was done while the writers were officers of the Medical Corps, United States Army, attached to Base Hospital No. 2 (organized by the Presbyterian Hospital of New York City), which had taken over No. 1 General Hospital, British Expeditionary Force, at Etretat, France.

Read at the meeting of the American Association of Genito-Urinary Surgeons, Atlantic City, N. J., June, 1919.

embolism. . . . . These cases, however, are few in number, and are quite different from the ordinary form of nephritis . . . . where dropsy is really the dominant physical sign.

Dunn and McNee (3) have called attention to a similar group of cases. Unfortunately no distinction of clinical types is made in their discussion of pathology. We cannot claim an identity between our cases and theirs, but the similarity is suggestively striking.

Although this condition has been noted by these writers and others, they have failed to dissociate it from "war nephritis," and have greatly underestimated its frequency, if our statistics be accepted as an indication of the general incidence of renal conditions as they occurred on the British Western Front. The result of a clinical analysis of 204 consecutive cases admitted to the Hospital with a diagnosis of nephritis or with an allied condition is given in the following table.

	NUMBER OF CASES	PER CENT
Chronic renal or cardio-vascular disease	91	44.5
Acute nephritis	75	36.5
Albuminuria during infectious diseases	6	3.0
Pan-urinary pyogenic infections (demonstrated by ureteral catheterization and urine culture)	4	2.0
Urinary tract purpura	18	9.0
Questionable urinary tract purpura	10	5.0
Total	204	100.0

Furthermore the descriptions in the literature which we have found have failed to call attention to the lower urinary tract symptoms that are such a striking feature in these cases, and nowhere have we found any reports of examinations of the bladder.

We are reporting thirty-seven[2] cases encountered in a period of eighteen months in France. Of these thirty-six were seen while working with the British Expeditionary Force, and one with the American Expeditionary Force. Twenty-six conform

[2] The records of the first case are so incomplete that this protocol has been omitted.

in all respects to the picture of the condition under discussion. Two were atypical in their course, but exhibited the usual bladder hemorrhages. Nine, in which no hemorrhages were found, presented a very suggestive clinical picture.

It may seem surprising that a disease of such frequency should have passed unrecognized so long. The explanation seems to lie in the fact that all the cases were early placed in other categories because of one or another prominent symptom. Examination of the case reports will show that about half were admitted with a diagnosis of "nephritis." The others were labelled "renal" or "vesical calculus," "hematuria," "albuminuria," "inflammation of the bladder," "influenza," or "pyrexia of unknown origin." Without the aid of the cystoscope these errors might never have been corrected, although we were later able to make a preliminary diagnosis with reasonable certainty from the symptoms without this special aid.

Before beginning our duties in France we had decided to study closely so-called "war nephritis" and the allied conditions with the hope that we might dissociate one or more diseases that differed from the types known in civil practice. As a preliminary we instituted merely a careful clinical analysis of all cases admitted to the hospital suggestive in diagnosis or symptoms of renal disorders. Early in the course of the work we received a patient with profuse hematuria who complained of symptoms strongly suggesting vesical calculus or papilloma. Cystoscopic examination by one of us revealed neither stone nor neoplasm, but, instead, multiple submucous hemorrhages in the bladder wall and blood pouring from both ureters. The unusual findings in this case led to the routine use of the cystoscope in all cases of hematuria. The frequency of the condition and the constancy of the associated syndrome soon became apparent.

ANALYSIS OF CASES

For the sake of clearness the twenty-five definite cases with protocols will be discussed first, as a group, and the last eleven will be considered separately later, as possible variants of the disease.

HISTORY OF PREVIOUS ILLNESS

No suggestion of any predisposing factor can be found in the histories of these patients. Two (nos. 11 and 17) had had diphtheria; two (nos. 11 and 15) rheumatic fever; and three (nos. 3, 12 and 22), recurrent attacks of tonsillitis: all without cardiac or renal complications. Eight (nos. 3, 6, 8, 14, 15, 19, 23 and 24) had noticed exceptional dyspnea, but in only three (nos. 14, 19 and 23) was this sufficiently severe to prevent the patient from "carrying on," even on route marches, with a pack. Four (nos. 8, 9, 11, and 17) gave a history of recurrent respiratory infections and one of these (no. 17) showed signs of chronic bronchitis. Three only (nos. 2, 3 and 25) had had gonorrhea and these showed no residual signs of the disease.

PRODROMATA AND ONSET

In eighteen cases the onset was sudden with a complete development of the disease within forty-eight hours. In seven of these, urinary symptoms were preceded for from twelve to forty-eight hours by general symptoms: headache, pains in the legs, malaise, weakness and giddiness. Seven patients exhibited, for a variable period, symptoms that bore no definite relation to the typical disease complex. No. 3 had an acute onset of urinary symptoms after seven days of increasing weakness; no. 5 after a fortnight of intermittent headache, nausea and vomiting; nos. 22 and 24 after three days diarrhea and general malaise. Nos. 12, 14 and 17 had symptoms of respiratory infection for about a week. Even in these cases, the actual development of the disease was extremely rapid and these preliminary symptoms may have been merely adventitious and not true prodromata.

The complete picture of the condition at onset showed marked prostration and general malaise, headache, pains in the legs and back, gross hematuria, frequency and urgency of urination, dysuria and pyrexia. The order of appearance of the symptoms varied as did their relative severity.

ANALYSIS OF SYMPTOMS

Those patients who were admitted during the febrile period of the disease approached in general appearance the picture of an acute infection; later the most striking features were pallor and general debility. The common signs and symptoms of nephritis were noticeably lacking. Only four (nos. 7, 11, 15, and 16) showed any edema and, in these cases, it was very slight and evanescent. Only three (nos. 7, 8, and 12) suffered from dyspnea, and then only on exertion during the febrile stage of the disease. All were completely free from uremic manifestations, unless one place in this category occasional nausea and vomiting.

The pains were of two types: those that seemed to be due to the effects of a general infection, and those that were referable distinctly to the urinary tract. The former presented themselves as severe headache and general pains that seemed to have a tendency to localization especially in the back and limbs and were not unlike the pains of trench fever. These usually ended with the cessation of the first bout of fever, but showed occasional sporadic recurrences later in the course of the disease, usually associated with slight elevation of temperature. Tenderness or hyperesthesia was often present over the painful areas, but was not always constant.

The urinary pains varied from dull aching in the lumbar region and the upper abdomen to the acute, lancinating pain of renal or vesical colic, and were usually attended by marked tenderness over the kidneys and bladder. These pains may have been due to the passage of blood clots, which were noted in one instance (no. 10). A very large proportion of the cases suffered from severe dysuria and frequency and urgency of urination, which usually ceased shortly after the disappearance of the gross hematuria, but occasionally persisted longer. These symptoms may be due to the presence of the hemorrhagic lesions themselves, or to the presence of some irritating substance in the urine.

Dizziness and extreme muscular weakness were sufficiently frequent to deserve notice. Three patients (nos. 3, 7, and 17)

actually fainted. In the early stages, these symptoms might be looked upon as concomitants of the fever, later as indications of an anemia. Herpes labialis occurred in five cases (nos. 1, 7, 9, 20 and 21), and in one instance (no. 9) became infected. With these exceptions, the skin and visible mucous membranes were clear, except for the usual pediculosis and scratch marks. Cutaneous, oral and conjunctival hemorrhages were never found in spite of repeated examinations; nor did ophthalmoscopic examinations reveal any changes in the fundus. No abnormalities of the reflexes, sensations and muscular strength were found.

Signs of respiratory disease were discovered in only five cases, and, in these, bore no evident relation to the urinary condition. In two (nos. 12 and 14) respiratory symptoms definitely antedated the urinary symptoms in their development. The third (no. 17) had a chronic bronchitis.

Eight patients had abnormal cardiac signs. Nos. 4 and 22 showed a transient enlargement of the area of cardiac dulness to the left; nos. 9, 10, 12 and 21, systolic murmurs without enlargement; and nos. 5 and 16, slight enlargement with a systolic murmur. There were no disorders of cardiac action. The blood pressure was never elevated above normal limits, although in two cases the radial arteries were definitely palpable.

In three instances (nos. 1, 22 and 24) there was an initial diarrhea, and in a few others occasional nausea and vomiting. No gross blood was found in either stools or vomitus. Otherwise there were no disturbances of the gastro-intestinal tract. The spleen was found enlarged twice (nos. 9 and 20); in no. 9 this occurred in the presence of an intercurrent infection of herpes labialis. The liver was never found enlarged either by palpation or percussion, nor was jaundice ever present.

In eight cases there was tenderness in one or both renal regions: the right kidney was felt once. The external genitalia were uniformly normal. The prostate and seminal vesicles showed evidences of inflammation on rectal palpation in two cases only, and these had no pus in the urine.

Only one patient (no. 10) was afebrile throughout the course of the disease. In most cases the initial temperature was quite

high, in one instance 103.8° (by mouth) while under our observation. Of course our records are incomplete, because we have but scant notes on the initial period of the disease. The temperature fell rather rapidly in most cases, but in some remained elevated for a considerable time. After the cessation of this initial pyrexia, all the patients had occasional elevations of temperature to 99° or 100° (by mouth) associated with general malaise and myalgic pains for an indefinite period. These temperature relapses were noted as late as the sixty-first day of the disease in one case. The pulse rate often remained elevated during the afebrile period. The temperature charts are appended with the case reports.

One case (no. 14) relapsed while under observation with a coincident recurrence of gross hematuria, dysuria and frequency, almost seven weeks after the onset of the illness. Another (no. 18), was admitted with an apparent recurrence after a free interval of seven weeks.

URINARY FINDINGS

All the patients exhibited gross hematuria in the early stages of the condition. This lasted from three to fourteen days. All but one (no. 10) showed casts at some time. Usually they were of the hyaline and granular types, but in at least seventeen cases cellular casts (epithelial and more frequently red blood cell casts) were present. Although gross blood did not persist very long, erythrocytes were observed as late as the sixty-third day of the disease in one case, and the fifty-ninth in another. Only occasionally was any considerable number of leucocytes seen, and never frank pus. Usually the appearance of leucocytes followed cystoscopic examination. Sometimes the urine became negative for a period, with a later recurrence of albumin and casts and red blood cells. In one instance (no. 14) there was a recurrence of gross hematuria while under observation. Albumin was seldom very marked; in most cases it could be fully explained by the amount of blood present.

No. 10 alone was discharged from the Hospital with consistently negative urinary findings and without symptoms. The majority

was evacuated to England, still showing a slight trace of albumin and casts; many showed microscopic blood persistently after the symptoms had disappeared. The termination of the period of observation varied from the eleventh day of the disease to the one hundred and eleventh. Although we have tried to follow these cases further by means of cards, we have received but few replies.

The only renal function test we were able to employ was the phenolsulphonphthalein test which was used in twenty cases. In all but four, there was a definite diminution in the excretion of the dye, the output varying from 13 per cent to 50 per cent in two hours. Where repeated tests were made, an improvement of function usually occurred with convalescence.

From the catheterized bladder urine of thirteen cases, staphylococci were obtained four times and a mixed growth of streptococci and Gram negative bacilli once; the other specimens were found sterile. Although the strictest precautions were observed, it is so notoriously difficult to obtain urine sterile, it seems safer to consider these as contaminations, especially as the organisms were seldom found in all the media used, and subsequent cultures from the same subjects proved negative when taken. The following media were used: broth, glucose-agar, hydrocele-glucose-agar and blood-agar. In six cases anaerobic cultures were also set up. In no cases were any organisms found in the smears of the urinary sediment, stained with methylene-blue and Gram.

Giemsa and Fontana stains failed to reveal the presence of spirochetes, and the injection of urine from three cases into guinea-pigs was equally unsuccessful.

EXAMINATION OF THE BLOOD

White blood cell and differential counts on ten patients showed so little uniformity that no conclusions can be drawn from them beyond the fact that there is, apparently, no leucocytosis. Late in the disease a slight secondary anemia was found, coinciding with clinical observation. In no. 12 this was considerable, the hemoglobin being 60 per cent and the red blood cell count

2,720,000 on the tenth day. No morphological changes were observed in the cells except some central pallor of the red corpuscles. No nucleated red cells were found.

Blood cultures were made in eleven cases. Two of these showed a few colonies of cocci on single plates only. These were not obtained on subsequent cultures and were probably contaminations.

Conditions did not permit a study of the chemistry of the blood or urine.

CYSTOSCOPY AND ENDOSCOPY

We undertook cystoscopic examinations of the earlier cases as a diagnostic measure to determine the origin of unexplained hematuria, associated with symptoms referable to the lower urinary tract. Multiple, fresh hemorrhages in the bladder mucosa, unassociated with inflammation, tumor or stone, were observed; and in those cases presenting gross hematuria at the time of cystoscopy, bloody urine was seen coming from both ureteral orifices. It was this striking and novel picture that led to this study. The impressions recorded in the earlier publicaton (1) need but little alteration to accord with our larger experience with these cases. As in the preceding paragraphs the statistics concern only the first twenty-five of the thirty-six protocols attached.

The initial cystoscopies were done from three to nineteen days after the onset of the illness. In all, essentially the same picture was found: multiple small hemorrhages into the bladder mucosa, unaccompanied by ulceration, neoplasm or calculus. Two cases had congestion of the whole bladder wall; otherwise there was no sign of inflammation in any instance. The hemorrhages numbered from two to over a hundred, and ranged in size from petechial spots to 1 cm. in diameter. The shape was usually irregular, and particularly so when neighboring lesions became confluent. They occurred chiefly on the posterior and posterior lateral walls of the bladder, and in nine cases involved the trigone, more frequently the proximal half. In no case was a hemorrhagic spot seen adjoining the margin of a ureteral orifice. Small petechiae

were noted four times on the anterior wall, but in every case lesions were found at the same time on the posterior wall. Very commonly it was noted that the hemorrhages were adjacent to or interrupted the course of visible blood vessels.

When gross hematuria existed at the time of cystoscopy, blood was clearly seen to come from both ureteral orifices. At no time did we note blood oozing from the bladder mucosa or issuing from the posterior urethra.

A second bladder examination was made in six of the twenty-five cases considered. In three, signs of some of the old lesions were present twelve to thirteen days after the first cystoscopy, although partially cleared up. In the other three instances, no signs of the original hemorrhages could be found. These latter observations were made eight, ten and twenty days after the initial cystoscopies. Contrary to the statement made in the preliminary report, we can record the occurrence of new bladder hemorrhages late in the course of the disease (no. 14, possibly no. 10).

Urethroscopy was done five times, and a good view of the posterior urethra obtained in four cases. Three of these presented well-defined hemorrhagic spots, all on the verumontanum.

Although we have made the presence of bladder hemorrhages the *sine qua non* for a diagnosis of the condition we are describing, in view of the fact that the bladder evidences have occurred chiefly at the onset of the disease and that these hemorrhages are absorbed rather quickly, it seems probable that this disease is more common than our figures show. Moreover, it is possible that the kidney, pelvis and ureter may alone be affected in some cases.

PATHOLOGIC REPORTS

We were able, by means of a small punch, operated through the cystoscope, to obtain specimens from the hemorrhagic spots in seven cases. On section these showed nothing absolutely characteristic. The mucosa was normal and unbroken. Where the bleeding had been recent, a profuse and patchy infiltration of well preserved red blood cells appeared in the submucosa.

There was no leucocytic infiltration and nothing suggesting an inflammatory lesion. The blood vessels were usually somewhat engorged. In one specimen, small nodular accumulations of degenerating connective tissue cells and wandering cells were found in the vicinity of the small arterioles, and there was indication of the formation of a mural thrombus in one of these vessels.

Two specimens from patients with hemorrhages of longer standing presented degenerative changes in the connective tissue cells of the submucosa and thrombosis of some of the medium-sized vessels.

The specimens were not entirely satisfactory because of their small size and the distortion resulting from the punch. If, as seems possible, the hemorrhages were due to vascular lesions, these lesions might not be included in such small bits. Unfortunately we had no bladder rongeur at our disposal with which we could remove larger specimens. That the changes observed were not due to mechanical factors we determined by comparison with specimens of normal bladder mucosa obtained from cases cystoscoped for other conditions. The lesions differed from the hemorrhagic spots obtained from a bladder which was the seat of cystitis in the fact that the latter showed a marked leucocytic infiltration.

Thus far the last eleven cases have been omitted from the discussion, because they differed in certain respects from the others. In nos. 26 to 34 inclusive, no hemorrhages were found in the bladder wall. Two of these (nos. 26 and 27) unfortunately escaped cystoscopy so that the absence of the distinctive lesions in these instances is not proved. In other respects they approximate very closely the clinical picture above described. Of course these hemorrhages are as yet the only really distinctive feature of the condition, but it is more than conceivable that cases may occur in which no lesions are found lower in the urinary tract than the kidney and ureters, just as there are others in which the lesions extend down as far as the urethra. Some additional support for such a contention is found in the fact that

positive urinary findings were so frequently met in the first 25 cases even when the bladder wall was entirely clear. Moreover, in these instances, the cystoscopic examinations may have been made during intervals in which affected bladders were free from hemorrhages. If this is so, the incidence of the disease may well be higher than our figures show.

In no. 35 typical hemorrhages were discovered in the bladder. However, his clinical picture is very complex and there is evidence that the hemorrhagic condition was not confined to the urinary tract, but involved also the cerebrum. No. 36 conformed to type only at the very beginning of his illness, when his symptoms were entirely confined to the urinary tract. Later he developed a general purpuric condition that was rapidly fatal. At autopsy non-inflammatory hemorrhages were found in his bladder wall. As this is the sign on which we must depend for a diagnosis at present, we do not feel justified in omitting either of these patients. Furthermore, it may be that we are dealing with a hemorrhagic disease which usually reveals itself only in the urinary tract, but in severe cases, also affects other organs.

The changes observed in the kidney of no. 36 are not out of keeping with the urinary findings in the other cases. The hemorrhages into the mucosa of the renal pelvis and in the tubules of the kidney are the lesions one would expect in cases which so regularly present bladder hemorrhages, gross hematuria and red blood cell casts. This case is in itself sufficiently striking to merit publication and gains added interest from the fact that the microscopic picture of the kidney section resembles closely one among those recently reported by Tytler and Ryle (4). Further comparison is impossible because their paper contains no protocols.

DISCUSSION

The consistent presence of casts in the urine and the reduction of renal function indicated by the phenolsulphonphthalein excretion seems to be sufficient evidence to justify us in assuming the presence of a definite renal lesion in these cases. On the other hand the disease differs in very essential respects from the ordi-

nary types of acute nephritis seen in civil life or among the admissions of a General War Hospital. The common symptoms of edema and dyspnea are almost entirely lacking as are uremic manifestations. Moreover, although we have cystoscoped thirty patients who had typical nephritis with hematuria, none of them has shown bladder hemorrhages, the most striking feature in our cases. The comparative absence of pus cells in the urine, the absence of leucocytic infiltration about the bladder lesions, and the consistently negative bacteriologic findings argue against the common forms of urinary infection due to pyogenic organisms.

The temperature and associated symptoms give one the impression of a general toxemia, probably of infectious origin. Our inability to find the responsible organism may be due to any one of several factors. The organism may be unsusceptible to isolation by ordinary cultural methods. It may not appear in any of the fluids of the body available for culture, or may appear only during certain periods of the disease. Except for the first cases, we were unable to study any patients during the really acute stage; usually by the time they had reached us both the high temperature and the gross hematuria had ceased. Work at a hospital in the front area might have been more successful and might have offered more material for pathologic study.

In many respects the disease resembles trench fever in its general manifestations. The pains and tenderness are often strikingly similar in nature and localization. The temperature course, with its relapsing or intermittent character is quite indistinguishable at times. However, in the last analysis, the diagnosis of "trench fever" is one that must be made by exclusion only, at present; and any attempt to establish even a remote relation on the basis of such non-distinctive symptoms seems quite unwarranted.

The evidence that we are dealing with a clinical entity is merely circumstantial; but the appearance in a considerable number of cases, of a distinctive pathologic and clinical syndrome hitherto unreported, is hardly conceivable as a fortuitous series of coincidences. The bladder hemorrhages cannot, at present be dis-

tinguished from any other purpuric lesions; but a purpura of such frequent occurrence, which is apparently limited, in at least a large proportion of cases, to the urinary tract, is sufficiently extraordinary to command attention. (Among the total admissions to the hospital during a period of eighteen months, only two other cases of purpura were found. One of these was of the Schoenlein type; the other, in many respects resembled the fatal case here reported (no. 36) and may have belonged to our group as he exhibited profuse hematuria. Unfortunately he was admitted early in the course of our study and was not cystoscoped.)

If this report be accepted as a description of a new disease, it detaches "urinary tract purpura" from the loose aggregation of conditions known as "war nephritis," a name which should give way to one or more definite disease titles and "acute nephritis," —that irreducible minimum of unexplained renal disturbances known to all our civil hospitals in peace.

We can find no evidence to indicate that this disease is dependent for its occurrence on any specific war conditions. It has been observed in men from all branches of the Service. It developed in one of the members of our own organization who had never been within one hundred miles of the front area and whose contact with patients had been minimal because of his duties as dental technician. It seems quite possible that this purpura of the urinary tract may be encountered also in civil life and may explain some obscure cases of so-called "essential hematuria."

We desire to express our appreciation of the help we received from other members of the hospital staff—particularly to Colonel H. F. Swift for his constant interest and assistance; to Major A. M. Pappenheimer for interpretations of the pathologic specimens; and to Lieutenant D. P. Barr who aided greatly in the clinical work.

CONCLUSIONS

1. This paper reports a group of cases that presented as a distinguishing feature a purpuric condition confined, in at least the majority of cases, entirely to the urinary tract. This con-

dition was marked by an acute onset, temperature of an irregular type, general febrile symptoms, frequency of urination, dysuria, gross hematuria, cylindruria and a reduction of the phenolsulphonphthalein excretion.

2. The disease, as far as it could be observed, tended to run a prolonged subacute or chronic course. Occasionally acute relapses occurred.

3. In all, 26 definite cases and 11 questionable cases were found in a period of 18 months.

4. This condition made up 14 per cent of all the medical renal cases and 28 per cent of the acute medical renal cases admitted to the Hospital over a period of ten months.

5. The presence of the disease was established in both the American and the British Expeditionary Forces.

6. Pathologic examination of the lesions obtained from the bladder wall by means of a cystoscopic punch revealed submucous hemorrhages unaccompanied by any signs of inflammation. Suggestive vascular changes were observed in some specimens.

7. Bacteriologic examination of blood and urine proved negative. Attempts to determine the etiology of this condition or to identify it with any known disease were unsuccessful.

8. We believe the condition here described is sufficiently distinctive to merit consideration as a new disease.

9. There is no direct evidence that its incidence is dependent upon the special conditions occurring in war. It seems quite possible that cases of this disease may occur in civil life.

REFERENCES

(1) Peters and Stevens: Journ. Am. Med. Assn., 1918, lxx, no. 23, 1760.
(2) Bradford, Rose: Quart. Journ. Med., Oxford, 1916, ix, 125, and Journ. of the Royal Army Medical Corps, October, 1916.
(3) Dunn and McNee: Brit. Med. Journ., 1917, no. 2971, 745.
(4) Tytler and Ryle: Quart. Journ. Med., Oxford, 1918, xi, 113.

PLATE 1

Four Cystoscopic Views of Hemorrhages in Bladder Mucosa, from Three Cases

A

B

C

D

PLATE 2

Hemorrhages in Bladder Wall

Fig. A. Low power, showing patchy nature of hemorrhagic infiltrations. Case no. 15.

Fig. B. High power of similar lesion, showing absence of inflammatory reaction. Case no. 12.

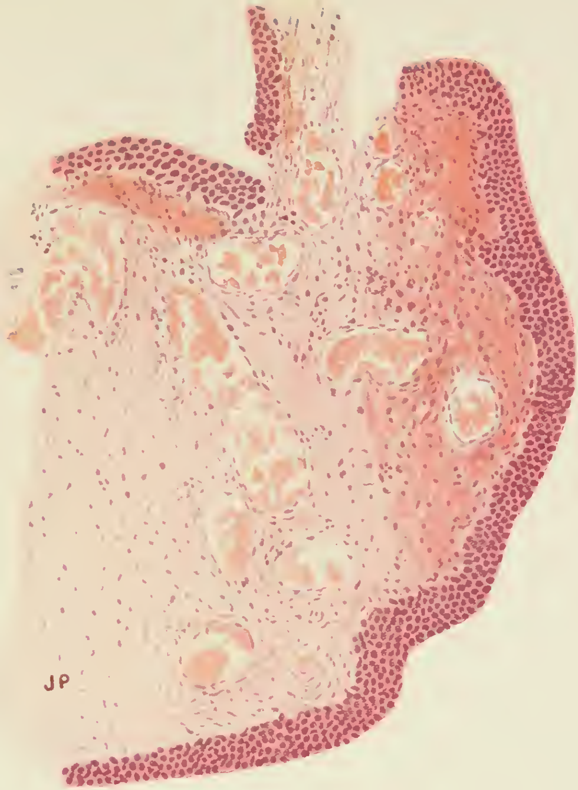


FIG. A

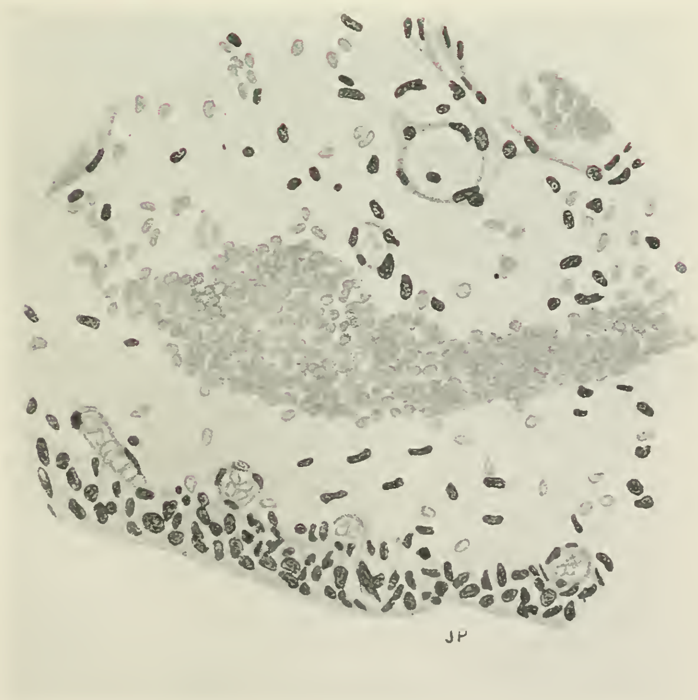


FIG. B

PLATE 3

Oil Immersion of Lesion in Small Arteriole in a Hemorrhagic Area.

Case no. 6

PLATE 3

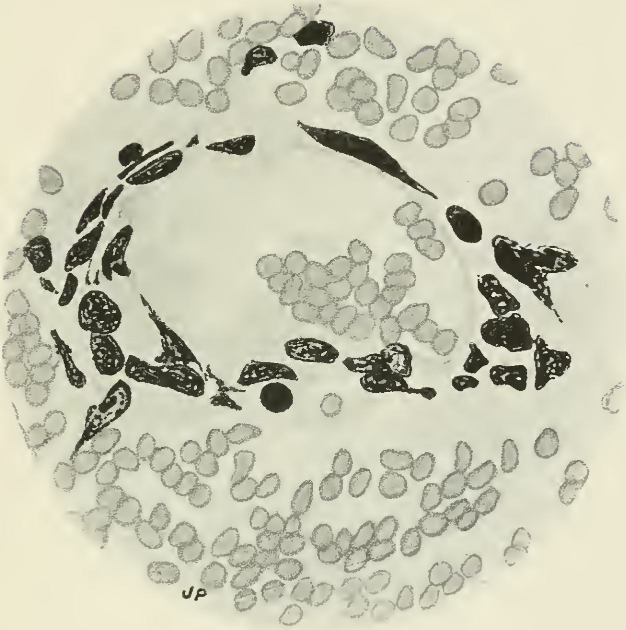


PLATE 4

CASE NO. 14, FEBRUARY 5, 1918, SHOWING THROMBI IN THE MEDIUM-SIZED VESSELS AND CHANGES IN THE CONNECTIVE TISSUE OF THE SUBMUCOSA. HEMORRHAGES ALMOST COMPLETELY ABSORBED

FIG. A. Low power field, showing two thrombosed vessels.
FIG. B. High power field, including one thrombosed vessel.

FIG. A

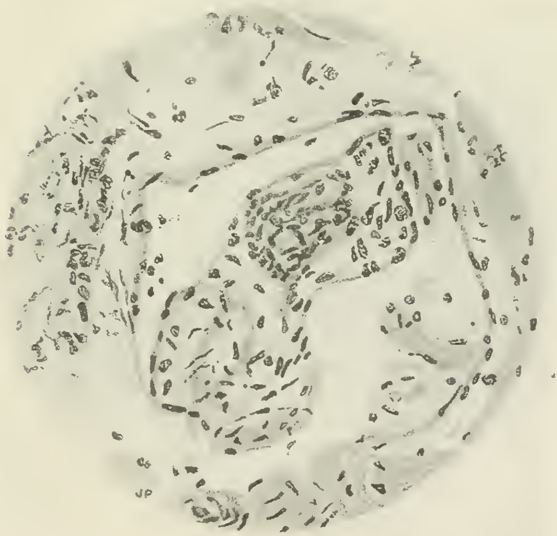


FIG. B

PLATES 5 AND 6

KIDNEY OF CASE NO. 26

FIG. A. Low power field, showing massive intratubular hemorrhages.
FIG. B. High power from same field.

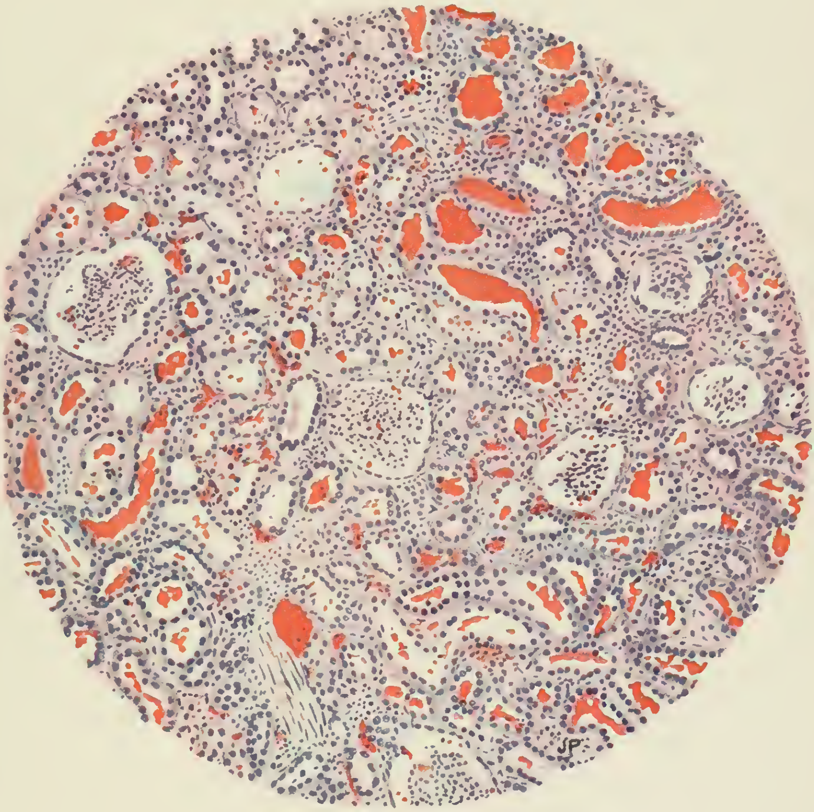


FIG. A

FIG. B

CASE REPORTS

Case I

Age twenty-six years. Infantryman. Total service three years. Field service six months.

Admitted: July 8, 1917.

Diagnosis on admission: Nephritis.

Past history:[3] The patient was a color mixer and worked with aniline dyes before he entered the Service.

Present illness: Began June 28, just after he had come out of the trenches, with headache, pains in the legs and general malaise. The next morning chilly sensations, diarrhea and temperature 103°. At the same time noticed that his urine was bloody. Bloody urine noted at Casualty Clearing Station on July 2. Diarrhea lasted only one day, but hematuria continued. July 1, pain on urination began. At no time did he have any shortness of breath or edema.

Physical examination on admission: The patient looked acutely ill, but seemed to be suffering no pain; was somewhat lethargic but perfectly clear mentally. No dyspnea or edema. No hemorrhages or other skin lesions, except herpes labialis. Teeth in very poor

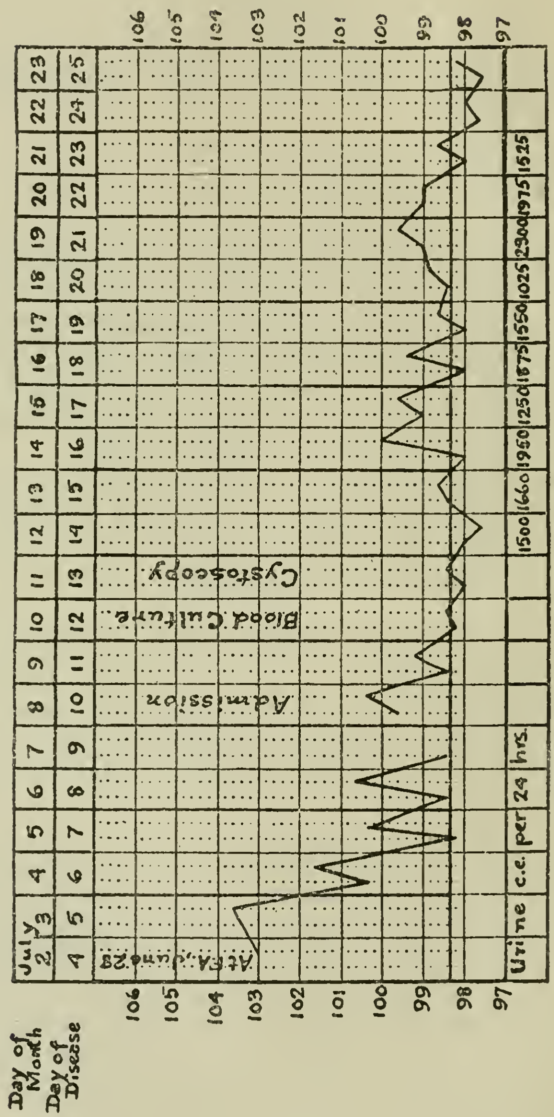
[3] In all histories, an attempt has been made to determine the presence of any conditions or diseases predisposing to cardiac or renal disease, previous diagnosis of heart or kidney affections and symptoms pointing to weakness of these organs. In all cases careful inquiries have been made for a history of scarlet fever, diphtheria, tonsillitis, rheumatism, dyspnea on exertion, orthopnea, palpitation, cardiac pain, edema, polyuria, nycturia, albuminuria and hematuria. The question of venereal diseases and addiction to alcohol has also been ascertained.

The previous occupation of the patient has been noted, as have previous rejections for the army. In the case of the latter an attempt has been made to determine whether the cause of the rejection was any cardiac or renal disorder. Finally we have enquired into the presence or absence of respiratory infection of any kind, at or immediately preceding the onset of the present illness.

In the study of the present condition, besides the regular chronological occurrence of symptoms, special questions have been asked with regard to the presence or absence of edema, dyspnea, orthopnea and other cardiac symptoms: headache, pains, syncope, coma, convulsions and other nervous symptoms; visual disturbances; chills and temperature; vomiting and diarrhea; oliguria, polyuria, frequency, nycturia, albuminuria, hematuria, dysuria and retention.

A systematic physical examination has been made in each case on admission and at intervals during the course of the disease.

For the sake of brevity, all negative findings will be omitted, except where, for the sake of emphasis, it seems advisable to report them.


Day of Month
Day of Disease
At F.A. June 28
Admission
Blood Culture
Cystoscopy
Urine c.c. per 24 hrs.

Case 1

condition; pyorrhea and gingivitis. Heart: apex and left border of cardiac dulness in the nipple line in the 5th space; no enlargement to the right; sounds of good quality; no murmurs or accentuations. Pulse 90, regular. Blood pressure: systolic, 128; diastolic, 76. Lungs negative. Slight tenderness in both costo-vertebral angles and in the umbilical area. Spleen, liver and kidneys not felt.

July 9. Stool culture: No organisms of enteric group isolated.

*Urine reports:** Amount of urine excreted measured from July 12 to 21 and found normal, varying from 1500 to 2300 cc. in twenty-four hours.

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
June 29		"Present"	"Blood present"		At Field Ambulance
July 2		"Heavy"	"Guaiac positive"		At Casualty Clearing Station
July 7	1012	++	+	+	0
July 11			+++	0	Cellular
July 30	1014	+	+	0	Few hyaline, many granular and occasional cellular

* For brevity, our analyses for albumin are reported as follows:

+ = precipitate visible only with the aid of black background (heat and acetic acid test).
++ = precipitate just visible without black background.
+++ = precipitate opaque.
++++ = precipitate beginning to flocculate.
+++++ = precipitate solid.

Microscopic red and white blood cells are roughly quantitated in a similar manner. Gross blood is reported in terms descriptive of the appearance of the urine. In recording examinations of urine made elsewhere, the original terms are retained.

July 10. Blood culture—one colony of Gram positive diplococci.

July 11. *Cystoscopic examination:* Several small hemorrhages scattered over the posterior and lateral walls of the bladder and some congestion at the base of the bladder. Culture of urine obtained through the cystoscope—bladder urine shows few colonies of staphylococci (probably contaminations); urine from left ureter gives no growth. Right ureter not catheterized.

Ophthalmoscopic examination negative.

Blood count: W. B. C., 6100; polynuclears, 62 per cent; lymphocytes, 34 per cent; large mononuclears, 4 per cent.

July 12. Blood culture sterile.

July 20. Blood pressure: systolic, 128; diastolic, 84. Patient feels entirely well.

August 1. Phenolsulphonphthalein excretion 60 per cent in two hours and ten minutes from the time of subcutaneous injection.[4]

August 8. Patient evacuated to England, free from subjective symptoms. Temperature has been normal for some days. Last urine examination showed some albumin and casts.

Case II

Age twenty-nine years. Infantryman. Total service seven months. Field service four months.

Admitted: July 8, 1917.

Diagnosis on admission: "Stone in bladder (?)."

Past history: Gonorrhea six years ago; no complications. In civil life a boiler maker.

Present history: Onset sudden, June 30, while in trenches, with backache, frequency of urination, terminal dysuria, and hematuria that was also for the most part terminal. No shortness of breath or edema.

Physical examination on admission: Does not appear acutely ill. Mental condition normal. No dyspnea or edema. Heart entirely negative. Pulse 72, regular and of good quality. Lungs and abdomen negative. Liver, spleen and kidneys not felt. No tenderness in abdomen or back.

There is more blood in the second urine voided than in the first, in the two glass test. Culture of catheterized specimen of urine sterile.

Cystoscopic examination: On the posterior and lateral walls of the bladder are hemorrhagic spots; otherwise the bladder wall is normal. No stones or tumors. Ureteral orifices normal.

[4] We have, in all cases, followed a simplified technique for the determination of the phenolsulphonphthalein excretion. No attempt has been made to determine the exact time of appearance of the color in the urine. Two hours and ten minutes after the subcutaneous injection of the usual dose (6 mgm.) of the drug, the patient is directed to void, and the color is determined in this specimen. Patients have not been catheterized.

July 23. Frequency reduced to every four hours during the day, and patient does not have to get up to void at night. Phenolsulphonphthalein, 45 per cent.

(Temperature record lost.)

Urine examinations

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 9.........	1020	+++	+++	+	Many hyaline and granular
July 10........		+	++	+	Many hyaline and granular
July 21........		0	0	0	

Case III

Age thirty-three. Infantryman. Total service eleven years. Field service two years and ten months.

Admitted: July 23, 1917.

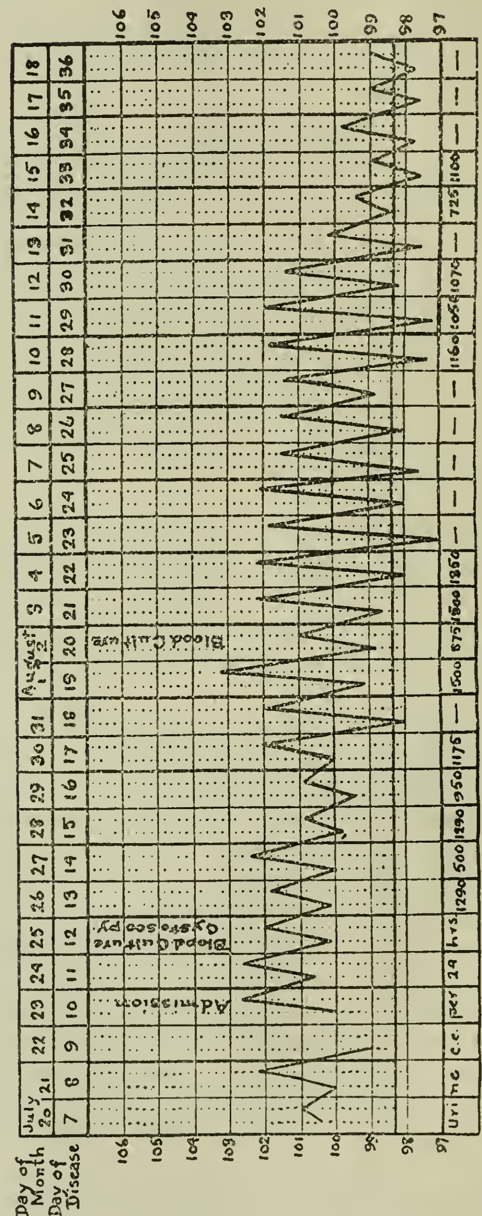
Diagnosis on admission: Hematuria.

Past history: Subject to frequent attacks of tonsillitis during the winter for years. For some time has suffered from shortness of breath when he carries his pack, and for the last two years has had to get up to urinate once every night. Has had gonorrhea, without complications.

Present illness: About July 14, noticed increasing weakness. July 20, while on duty, he fainted, and was admitted to the Field Ambulance. On recovering consciousness had severe headache and pains in the legs. He also noticed frequency of urination and dysuria. Field Ambulance reported profuse hematuria, and temperature 101°. Temperature and hematuria still present July 23.

Physical examination on admission: Appears acutely ill; somewhat stuporous, but mentally clear. No hyperpnea or edema. No signs of hemorrhages in the skin or visible mucous membranes. Lungs negative. Heart: apex beat felt 1 cm. to the left of the nipple line in the 5th space; left border of dulness lies in the same line; no enlargement to the right; sounds of good quality; no murmurs or accentuations. Pulse 90, regular and soft. Blood pressure: systolic, 124; diastolic, 76. Abdomen: tenderness in the upper part and in the right lumbar region.

July 25. Cystoscopic examination: Hemorrhages on the lateral and posterior walls, varying in size from minute points to 1 cm. in diameter,


Day of Month
Day of Disease
Admission
Blood Culture
Cystoscopy
Blood Culture
Urine c.c. per 24 hrs.

Case 3

and in color from bright red to deep brown. Both ureteral orifices normal and easily catheterized, 15 cm. Clear urine obtained from both kidneys.

Urine from both ureters shows very few granular casts, many red blood cells and epithelial cells, few leucocytes.

Cultures of urine from bladder and both ureters sterile.

No tenderness over kidneys; neither kidney palpable. External genitalia, prostate and seminal vesicles normal.

Phenolsulphonphthalein, 35 per cent.

Blood culture, sterile.

Blood count: W. B. C., 11,600; p.m.n., 52 per cent; lymphocyte, 42 per cent; large mononuclears, 2 per cent; transitionals, 4 per cent.

July 31. Steady clinical improvement. Today temperature normal for first time. Complains of sharp, sticking pain in region of cardiac

Urine examinations

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 23...............	1025	++++	++	++	Present
July 30...............	1015	+++	+	++	Many granular
August 7............		+	0	0	0
August 13...........			+	0	Many hyaline and granular
August 21...........		++	+	0	0
September 5..........		0	+	+	Many hyaline and granular
September 9..........		+	0	0	0

apex. Heart: not enlarged; left border 1 cm. inside left nipple line; no murmurs or accentuations. Lungs clear. Blood pressure: systolic, 118; diastolic, 76. Phenolsulphonphthalein, 40 per cent.

August 2. Blood culture sterile.

August 6. Still complains of some pain in the chest. No evidences of cardiac or pulmonary lesion.

August 7. Some pain and tenderness in left costo-vertebral angle.

Blood count: W. B. C., 8900; p.m.n., 39 per cent; lymphocytes, 50 per cent; large mononuclears, 1 per cent; transitionals, 9 per cent; basophiles, 1 per cent.

August 9. Blood smear shows no malarial organisms.

August 14. Complains of no symptoms except general malaise at night. Urine culture: diphtheroid and staphylococci (probably contaminations).

August 27. Complains of shooting pains in shoulders at night.

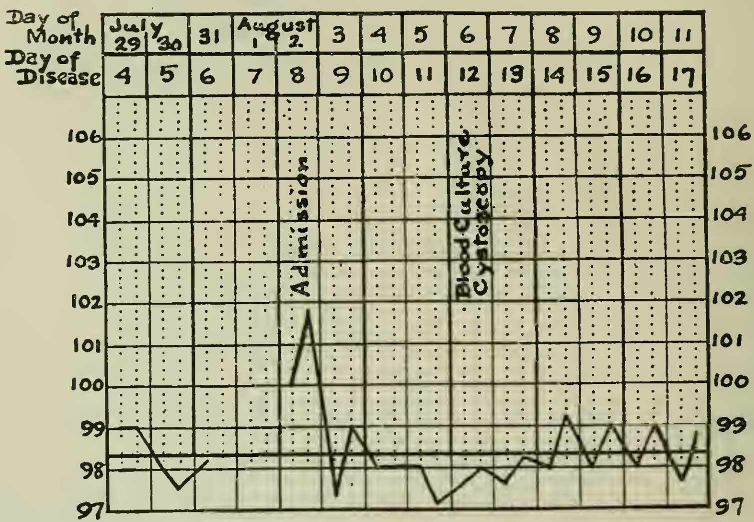
August 29. Feels perfectly well. Blood pressure: systolic, 124; diastolic, 84.

September 11. Phenolsulphonphthalein, 57 per cent.

Case IV

Age thirty years. Artilleryman. Total service twenty months. Field service ten months.

Admitted: August 2, 1917.



CASE 4

Diagnosis on admission: Hematuria.

Past history: Was a clerk before entering the service.

Present illness: Began July 26 with extreme weakness, headache, pains in the shins and the backs of the knees, fever and hematuria. No edema or shortness of breath. No frequency or dysuria.

Physical examination on admission: Appears acutely ill, but seems to be suffering no pain. No edema or hyperpnea. Is mentally clear. No visible hemorrhages in skin or mucous membranes. Lungs, abdomen and extremities entirely normal. Heart: apex beat in the 5th space in the nipple line; left border of cardiac dulness just outside the nipple line; no enlargement to the right; the sounds are of good quality;

no murmurs or accentuations. Pulse 78, regular, of good quality. Blood pressure: systolic, 126; diastolic, 58.

August 5. For three days has complained of pains in shins and shoulders, worse at night.

August 6. Cystoscopic examination: The whole surface of the bladder looks bright red and the vessels appear more prominent than normal. There is an aggregation of minute bright red spots on the right posterior wall, evidently clearing hemorrhages. Ureteral orifices normal. External genitalia, prostate and seminal vesicles normal.

Culture of urine sterile.

Blood culture shows a streptoccocus or pneumococcus producing green on blood plates, giving diffuse clouding in broth, doubtfully bile soluble, and not showing a definite capsule. This appeared in one flask only, another flask and all plates were sterile—(probably contamination).

Phenolsulphonphthalein, 55 per cent.

August 8. Allowed up. Feels entirely well.

August 10. Complains of some pains in shins again.

August 14. Feels entirely well; evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 2	++++	+	+	Present
August 6	+	++	0	0
August 7		+	0	Few hyaline and cellular
August 13	0	0	0	0
August 16	+	+	0	0

Case V

Age thirty-eight years. Machine Gun Corps. Total service twenty months. Field service four months.

Admitted: August 4, 1917.

Diagnosis on admission: Albuminuria.

Past history: Was an accountant in civil life.

Present illness: For two or three weeks before reporting ill was troubled with headache and nausea, and vomited every two or three days. On July 31 was suddenly seized with urgency and frequency of micturition, pain before, after and during urination. Reported sick and was taken to the Field Ambulance and from there to the Casualty

Clearing Station the same day. At the Field Ambulance, albumin in large quantity, but no blood, was found in the urine. At the Casualty Clearing Station blood was found in the urine. Has had no shortness of breadth or edema at any time.

Physical examination on admission: Still complains of urgency and pain on urination. Looks pale, but not actually ill, and seems to be suffering no pain. Mentally perfectly clear. No edema or hyperpnea. Lungs, abdomen and extremities entirely negative. Heart: apex beat in the 5th space, 1 cm. to the left of the nipple line; cardiac dulness extends from the right sternal margin to a point 2.5 cm. to the left of the nipple line in the 5th space; there is a faint systolic murmur at the apex, not transmitted. Pulse 72, regular, of good quality. Blood pressure: systolic, 122; diastolic, 86. No hemorrhages in skin or mucous membranes.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 31	"Large quantity"	"No blood present"		
August 2	"Present"	"Present"		
August 4	++++	"Gross blood"	0	
August 6	++++	"Gross blood"	0	
August 13		+++	+++	Many granular and cellular
August 24		+++	+++	Many granular
August 25	++	++	+++	Granular and cellular
August 30	+	+++	+	Great many hyaline, granular and cellular
September 5	+	+	+	Few granular, hyaline and cellular
September 9	++	++	++	Many granular

August 7. Pain less today, but frequency of urination has not diminished. Prostate boggy, but not especially tender. Seminal vesicles a little distended, but not indurated.

August 8. Cystoscopic examination: Distinctly bloody urine is seen coming from both ureters. There are many hemorrhagic patches, irregular in contour, scattered over the posterior and lateral walls of the bladder. Possibly slight congestion of the posterior wall, but

ureteral orifices are normal. The hemorrhages are not placed especially about the ureteral openings.

August 10. Pain on urination practically gone. Frequency continues; urination about every forty-five minutes; only small amounts are passed each time. Last night he had a slight attack of cardiac palpitation. The apex beat is heaving in character, 2.5 cm. beyond the left nipple line. No murmurs or accentuations. Pulse quite rapid. Phenolsulphonphthalein, 47 per cent.

August 14. Frequency continues, without pain. Catheterized urine shows profuse growth of staphylococci on blood plate; no growth on other media; no organism found in smears.

August 24. Now has to get up only once a night to urinate.

August 29. Symptoms entirely gone. Blood pressure: systolic, 126; diastolic, 84. Ophthalmoscopic examination negative.

September 10. Phenolsulphonphthalein, 48 per cent. Evacuated to England.

Temperature: No records before admission to hospital. Occasional elevations to 99° and 99.2° while in hospital.

Case VI

Age twenty-three years. Infantryman. Total service eighteen months. Field service six months.

Admitted: August 17, 1917.

Diagnosis on admission: Hematuria.

Past history: Some shortness of breath on long marches. Was a laborer in civil life.

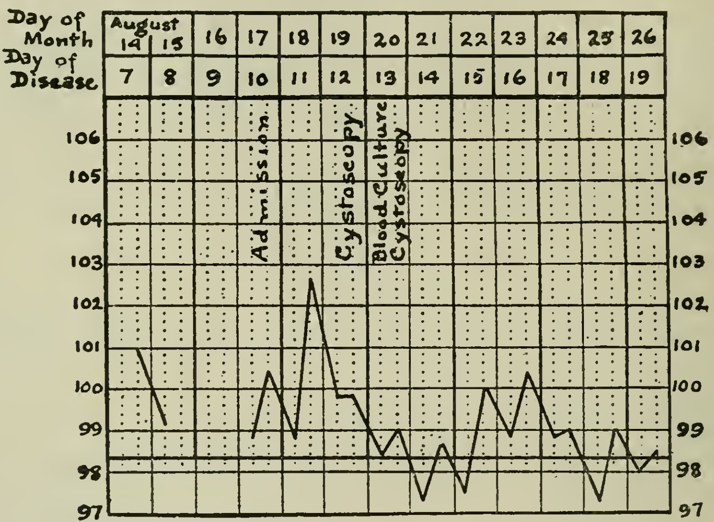
Present illness: Began August 11, six weeks after he had left the trenches, with headache, pains in the legs, hematuria, terminal dysuria and frequency of urination. He was forced to urinate as much as eight times each night at the beginning of his illness, passing only small amounts each time. No dyspnea or edema at any time. Was admitted to the Field Ambulance on the 14th, where a gross hematuria was reported, the blood being well mixed with the specimen. At that time also complained of severe headache and had a temperature of 101°.

Physical examination on admission: Does not appear acutely ill and seems to be suffering no pain. Somewhat pale. No edema or hyperpnea. The skin and mucous membranes clear, and present no signs of hemorrhages. Lungs and abdomen entirely negative. Liver,

spleen and kidneys not felt. No tenderness in back or legs. Heart: no enlargement, murmurs or accentuations. Pulse 78, regular and of good quality. Blood pressure: systolic, 110; diastolic, 74.

August 18. Phenolsulphonphthalein, 20 per cent.

August 19. *Cystoscopic examination:* The urine is slightly smoky. There are fresh hemorrhages scattered over the posterior wall and the posterior portion of lateral walls of the bladder. There is also one on the anterior wall. In some places these are seen to be composed of small fresh, almost punctate hemorrhages along the course of the vessels and interrupting the latter. In other cases there are big



Case 6

splotchy hemorrhages with scattered small hemorrhages about them. There is entire freedom from congestion and no signs of inflammation about the hemorrhages. The ureteral orifices are not seen, but the region about their usual site is entirely normal. Several of the hemorrhagic spots are along the left border of the trigone, but the trigone is not affected more than the rest of the posterior and lateral walls of the bladder. External genitalia, prostate and seminal vesicles normal. Kidneys not felt; no tenderness about them.

Culture of urine sterile.

Today complains of severe pains in shins.

August 20. Cystoscopy: Three specimens of bladder mucosa removed through the cystoscope with a punch, for pathologic examination.

Blood count: W.B.C., 6100; p.m.n., 52 per cent; lymphocytes, 46 per cent; large mononuclears, 1 per cent; transitionals, 1 per cent.

Blood culture sterile.

August 28. Phenolsulphonphthalein, 40 per cent.

August 29. Blood pressure: systolic, 136; diastolic, 82. Ophthalmoscopic examination negative.

October 8. Complains of pain low down in lumbar region. Physical examination still entirely negative except for a continuation of the pallor noted on admission. Patient discharged, still showing positive findings in the urine.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 14.......	"Present"	"Gross blood"		At Field Ambulance
August 17.......	++++	++	+	Granular, hyaline and cellular
August 30.......	+	+	++	Many granular and hyaline. Epithelium
September 5....	+++	+	+	Granular casts and cylindroids
September 14...	++++	+	+	Occasional granular
October 2.......	++	+	0	Occasional granular
October 8.......	++	++	0	No casts. A few epithelial cells

Ophthalmoscopic examination entirely negative.

Pathologic report on sections from the bladder wall: Small fragments of bladder tissue excised with the bladder punch, fixed with Zenker and stained with Giemsa and with Wright stains.

Microscopic examination (by Captain Pappenheimer): The tissue is covered over for the most part by normal epithelium, showing numerous mitotic figures. The underlying tissue is infiltrated profusely with well preserved red blood cells and collagen fibrils, forced apart by edema. Deeper down the tissue is firm and a striking lesion presents itself in the form of small nodular cell accumulations situated in the vicinity of the small capillaries. One of these is especially distinct and shows, under the high power, the following picture:

There is a mass of distorted nuclei, some are drawn out into long wisps and are hyperchromatic, others small, deeply stained and apparently pigmented. These nuclei belong in part to degenerating connective tissue cells and in part to wandering cells, some small lymphocytes and others impossible to identify. There are one or two eosinophilic polynuclears and reddish granules, resembling eosinophilic granules, scattered among the degenerating nuclei. The nodule reaches the lining of the vessel and causes a rounded prominence over which the endothelial cells show a marked alteration, the nuclei being irregular and pyknotic, and the cytoplasm less distinct than that in the normal endothelial cells lining the rest of the vessel. In a Giemsa stain no definite organisms were seen, but there is a group of purplish staining granules, probably part of the cytoplasm of a mast cell. Gram stains also revealed no organisms.

Case VII

Age twenty-six years. Infantryman. Total service twenty months. Field service seven months.

Admitted: August 21, 1917.

Diagnosis on admission: Nephritis.

Past history: Was rejected for the army in 1915, but does not know why. Worked in munitions for two years before entering the army; before that was a hotel manager.

Present illness: Began on August 11, while he was in the trenches, with headache, pain in the back, terminal dysuria and frequency of urination. He voided urine as often as three times during the night, passing only small amounts each time. He also noticed slight swelling of the face and some dyspnea on exertion, and felt very weak. Fainted twice the first day. He has had no extension of the edema and has not fainted again. Albumin noted at Field Ambulance, August 12; at Casualty Clearing Station, August 18. Gross hematuria first appeared August 18. Pain in back and headache persisted until August 21.

Physical examination on admission: Does not appear acutely ill. Seems to be suffering no pain, but complains of frequency of urination and pain on micturition, mostly terminal. No hyperpnea or edema. Except for some herpes labialis the skin and mucous membranes are entirely clear. Lungs and abdomen entirely negative. Liver, spleen and kidneys not palpable. No tenderness in back or legs. Heart: the apex impulse is found in the 5th space in the nipple line; the area of cardiac dulness extends from the right border of the sternum in the

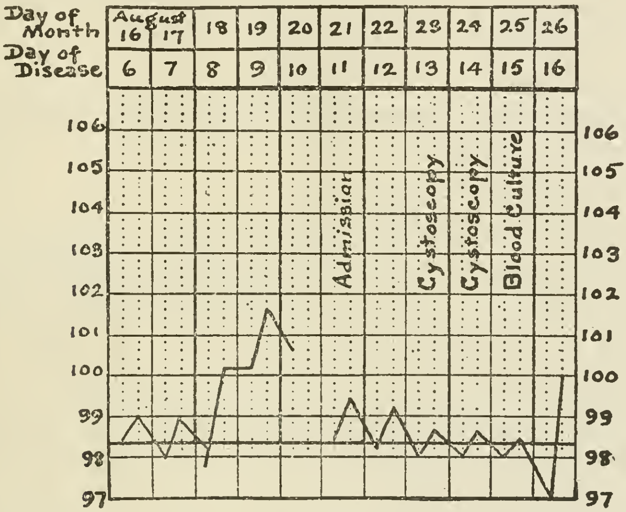
4th space to the left nipple line in the 5th space; no murmurs or accentuations; sounds of good quality. Pulse 84, regular. Blood pressure: systolic, 136; diastolic, 68.

August 23. Cystoscopic examination: Small, multiple, fresh hemor. rhages appear along the vessels on both lateral walls of the bladder- There is one large hemorrhage on the posterior wall, just above the trigone.

The ureteral orifices and the trigone are normal.

External genitalia, prostate and seminal vesicles are normal.

Kidneys neither palpable nor tender.



CASE 7

August 24. Cystoscopy and removal of specimens from the bladder mucosa with punch.

Culture of urine shows profuse growth of staphylococci.

August 25. Blood culture sterile.

Blood count: W. B. C., 17,600; p.m.n. 76 per cent; lymphocytes, 24 per cent.

August 28. Phenolsulphonphthalein, 45 per cent. Patient found to be a meningococcus carrier and therefore transferred to another hospital. Did not develop meningitis.

Pathologic examination of sections from the bladder mucosa reveals no inflammatory lesion. The mucosa is normal. The underlying

tissue is slightly edematous and shows a profuse infiltration with well preserved red blood cells. No leucocytic infiltration. The vessels are somewhat dilated, but show no lesions.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 12.......	"Present"			From Casualty Clearing Station
August 21.......	++	+++	+++	Many granular
August 24.......		+++	+++	Many granular and cellular. Many epithelial cells

Case VIII

Age thirty-two years. Infantryman. Total service seven months. Field service four months.

Admitted: October 3, 1917.

Diagnosis on admission: Nephritis.

Past history: Had bronchitis three times before joining the army. For two years has had some shortness of breath on exertion, but has been able to "carry on." He was a machinist in civil life. In 1916 he was rejected for the army, but does not know the reason. Since coming to France, he has done heavy labor in the front area. Had a cough and cold just before the onset of the present illness.

Present illness: Began September 30, with general pains and malaise. On the same day he was seized with urgency and frequency of urination and pain in the end of his penis when he passed urine. He also had severe headache and pains in the back. Later he developed some shortness of breath. No swelling of the face or extremities. Complained of some dizziness and blurring of vision.

Physical examination on admission: Appears acutely ill. Very pale. No hyperpnea or edema, but the face looks very pasty. No hemorrhages in the skin or mucous membranes. Lungs and abdomen entirely negative. Liver, spleen and kidneys not felt. Some tenderness in both costo-vertebral angles, and slight general abdominal tenderness, without resistance and with no palpable masses. Heart: apex beat neither visible nor palpable; the area of cardiac dulness extends from a point 2.5 cm. to the right of the sternum in the 4th space to the left nipple line in the 5th space; no murmurs or accentuations. Pulse 72, regular. Blood pressure: systolic, 132; diastolic, 98.

Ophthalmoscopic examination reveals a considerable degree of myopia but the fundus is entirely normal.

October 4. Still complains of abdominal pain. Severe constipation.

October 5. Cystoscopic examination: Five or six tiny hemorrhages along the course of the vessels on the right posterior wall of the bladder, and one on the left anterior wall. The rest of the bladder is entirely normal. The urine voided at the time of cystoscopy is clear.

External genitalia, prostate and seminal vesicles normal. The abdomen is held rather stiff. There is some tenderness in the region of the kidneys, but the kidneys cannot be felt.

October 8. Phenolsulphonphthalein, 35 per cent.

October 26. Does not seem to improve. Looks pale and chronically ill. Skin very pasty. Heart: rapid, but not enlarged; no murmurs or accentuations. Blood pressure: systolic, 136; diastolic, 96.

October 27. Phenolsulphonphthalein, 45 per cent.

November 5. Cystoscopic examination: Bladder mucosa entirely normal.

November 12. Patient discharged, without any real improvement in his condition.

Temperature: No record before admission to hospital. Temperature not above 99° while in hospital.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
October 11......	+	+++	+	Many hyaline and granular. Epithelium
October 18......	+	+++	+	Few hyaline
November 5....	+	+	+	Occasional granular. Epithelium

Case IX

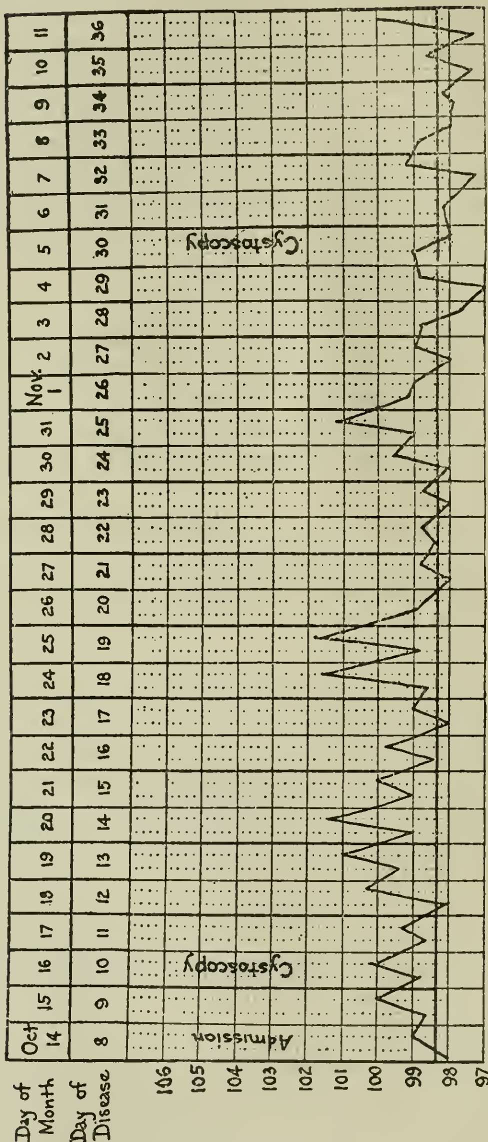
Age twenty-one years. Infantryman. Total service three years. Field service eleven months.

Admitted: October 14, 1917.

Diagnosis on admission: Nephritis.

Past history: Was a bookkeeper before the war.

Present illness: Began October 7 with giddiness. In the morning of the 8th he had general pains, and in the course of the day several attacks of chilliness without definite rigor. The next day the chilliness and general pains continued, and were associated with weakness and


Day of Month
Day of Disease
Admission
Cystoscopy
Cystoscopy

Case 9

severe headache. Has had frequency of urination and hematuria since the onset but no dysuria or retention. Has improved under treatment. Since October 10 has developed sores on his upper lips and both nostrils. Now suffers only from pain in the right hypochondrium and slight headache.

Physical examination on admission: Looks acutely ill. Patient appears rather flushed. No hyperpnea or edema. There are crusted lesions covering both nostrils, herpetic in origin, and extending along the sides of the nose, the upper lip and the right corner of the mouth. Otherwise the skin is clear. Nowhere in the skin or mucous membranes are there any hemorrhagic lesions. Lungs and abdomen entirely negative. Liver and spleen and kidneys not felt. No areas of tenderness or masses. Heart: not enlarged; soft systolic murmur at the apex, heard also over the pulmonic area. Pulse 72, regular. Blood pressure: systolic, 130; diastolic, 82.

October 16. Cystoscopic examination: The bladder wall shows groups of blotchy hemorrhages along the vessels. Twenty independent spots appear on the posterior wall, high up on the lateral walls, and about the trigone.

External genitalia, prostate and seminal vesicles normal.

October 17. Ophthalmoscopic examination: retinae entirely normal; no hemorrhages.

Vomited this morning. Tenderness in left hypochondrium persists. Spleen definitely palpable.

October 20. Left side of upper lip shows several pustules at the base of the hair follicles, with considerable redness, induration and tenderness. Herpes evidently infected.

Phenolsulphonphthalein, 40 per cent.

October 26. Blood pressure: systolic, 112; diastolic, 76.

October 27. Phenolsulphonphthalein, 50 per cent.

October 29. The infected herpetic area has practically cleared up, after incision and drainage.

October 31. Still complains of pain in the left hypochondrium, and headache. Temperature elevated last night. Lip entirely well. Spleen not felt. Pulse rapid, regular and flapping. Heart: not enlarged; soft, systolic murmur, audible at apex; sounds are everywhere weak and valvular in character.

November 5. Cystoscopic examination: All the hemorrhages found at the last examination have disappeared and the bladder mucosa is entirely normal.

November 12. Patient has gained weight and strength, but still complains of general pains. Discharged to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
October 11	++	0	0	Hyaline and granular
October 16	+	++	0	Moderate number of granular
October 26	+	++	++	Cellular and granular
November 6	+	0	0	Hyaline and granular

Case X

Age twenty-nine years. Orderly to the dental specialist of this Unit. Total service five months. Field service four months.

Admitted: October 12, 1917.

Diagnosis on admission: Renal calculus.

Past history: Patient was born in Armenia but has spent the last few years of his life in the United States. He was a dental technician before he entered the Service.

Present illness: On the morning of October 12, he was suddenly seized with severe pain in the left lumbar region, not radiating. The pain was paroxysmal and intense. It continued throughout the day. After his admission to the hospital it changed somewhat in character, radiating forward into the abdomen. When seen he showed no physical signs except moderate tenderness localized in the left side of the back, just outside the outer border of the erector spinae, below the 12th rib. The heart was not enlarged, but there was a soft, systolic murmur at the apex. Lungs negative.

The urine showed many red blood cells and a few small clots.

October 13. Local pain, referable to the left kidney has subsided but patient complains of some general abdominal pain and terminal dysuria. The urine contains gross blood which seems to be passed largely in the last portion of the urine voided.

October 14. Urine examination negative microscopically.

October 15. Radiograms of kidney and bladder regions negative. Pain has completely ceased.

October 16. Pain in the side has ceased, but the dysuria still continues, associated with frequency of urination.

Cystoscopic examination: There are numerous hemorrhages over the posterior and lateral walls of the bladder. The ureteral orifices are

normal. Wax-tipped catheter passed 30 cm. up the left ureter, but no scratch marks obtained.

October 17. Frequency of urination, urgency and terminal dysuria continue. A small amount of blood is passed at the end of urination, with occasionally a small clot. Some constant suprapubic pain.

Blood culture sterile.

Blood count: W. B. C., 10,900; p.m.n., 57 per cent; lymphocytes, 39 per cent; large mononuclears, 2 per cent; transitionals, 2 per cent.

October 18. There is some tenderness in the bladder region.

October 19. Phenolsulphonphthalein, 55 per cent.

October 26. Pain in the legs last night. Some tenderness along the anterior surface of the left thigh. Some pain at intervals in the left

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
October 12......	++	"Smoky and clots"	0	0
October 13......		"Gross blood"		
October 14......	++	0	0	0
October 17......	+++	+++	0	0
October 18......	++	+	+	0 (Urine in the morning red and smoky)
October 22......	0	+	0	0
October 31......	0	0	+	0
November 7....	0	0	0	0
November 9....	0	0	0	0

lumbar region and in the left hypochondrium, increased by deep breathing. Lungs negative. Heart: the apex impulse is in the nipple line; there is a soft systolic murmur at the apex. Blood pressure: systolic, 134; diastolic, 88.

Ophthalmoscopic examination negative.

October 28. Cystoscopic examination: Shows a persistence of the hemorrhages. There are some on the anterior wall on the left side, some on the posterior wall and along the borders of the trigone. None appears very fresh.

November 25. Gaining strength constantly. Has vague pains all over, but no definite symptoms. Urine normal. Discharged from the hospital.

Temperature: Records show no elevation above normal.

Case XI

Age thirty-five years. Infantryman. Total service one year. Field service four months.

Admitted: December 8, 1917.

Diagnosis on admission: Nephritis.

Past history: Diphtheria at age of nine. Rheumatism in 1900, no complications. Has had influenza twice.

Present illness: Began November 29 with shivering, hot flushes and general pains. He noticed that his urine was colored a chocolate brown. He had marked dysuria referred to the penis, and frequency of urination, passing only small amounts each time (had to get up as often as five times in the night). Was a little short of breath on exertion. The medical officer told him, when he reported sick, that he had some swelling of the legs. At that time he had a severe headache.

Physical examination on admission: Appears chronically ill. No hyperpnea or edema. Skin pasty. No hemorrhages found in the skin or mucous membranes. Lungs and abdomen negative. Heart: no enlargement; the sounds are very loud over the base of the sternum, but can hardly be heard at the left border of the heart; no murmurs or accentuations.

December 10. Cystoscopic examination: The bladder urine is perfectly clear. The bladder mucosa is entirely normal except for about 15 to 20 punctate hemorrhages along the lines of the vessels on the posterior and both lateral walls of the bladder. Ureteral orifices normal. External genitalia, prostate and seminal vesicles normal. The kidney regions are normal and the kidneys cannot be felt.

December 11. Blood pressure: systolic, 130; diastolic, 95.

December 13. Has had slight nausea and headache in the morning since admission. Hemoglobin, 90 per cent.

Phenolsulphonphthalein, 15 per cent.

December 15. Blood pressure: systolic, 120; diastolic, 85. Phenolsulphonphthalein, 15 per cent.

December 18. Cystoscopic examination: No signs of hemorrhages. One suspicious spot was seen on the posterior wall, but this was later removed with the cystoscopic punch, and proved to be not a hemorrhage but a small papillomatous hemangioma.

December 19. Phenolsulphonphthalein, 20 per cent.

January 9, 1918. Phenolsulphonphthalein, 30 per cent.

No symptoms.

February 4. Improvement in general condition has been continuous. Urine examinations have been entirely negative for a long time. Still looks pale and somewhat anemic.

February 16. Phenolsulphonphthalein, 55 per cent.

February 23. Blood count: Hemoglobin, 80 per cent; R.B.C., 4,750,000; W.B.C. 9,000; p.m.n. 44 per cent; lymphocytes 51 per cent; large mononuclears 1 per cent; transitionals 2 per cent; eosinophiles 2 per cent.

March 3. Phenolsulphonphthalein, 48 per cent.

March 4. Looks well nourished and developed but rather pale. Feels well except for slight cold. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse 72, regular. Abdomen negative except for slight tenderness in right costo-vertebral angle. Blood pressure: systolic, 136; diastolic, 94.

March 5. Discharged to England.

March 19. Report from patient in England. Had been kept in bed, on a fish diet, since arrival in hospital in England. Repeated examinations of urine showed albumin constantly present.

Temperature: No records before admission to hospital. 99.8°, December 11, 99.6°, December 23; otherwise not above 99°.

Urine examinations

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
December 8...		++	0	0	Few hyaline
December 11...		+	0	0	Few hyaline and granular
December 19...	1012	++	+++	0	Many hyaline, granular red blood cell casts
December 27...	1012	0	0	0	0
January 1......		0	0	0	0
March 4.......		+	+	+	Hyaline
March 19.......	Albumin still present (report from England)				

Case XII

Age twenty-five years. Battalion medical officer. Total service two and a half years. Field service twenty-six months.

Admitted: January 3, 1918.

Diagnosis on admission: Acute nephritis.

Past history: Was formerly subject to rather frequent attacks of tonsillitis. Was quite well until the third week of December, 1917,

when he began to suffer with a cough. "Carried on" with the battalion in the line, however. After two days felt better. Then came out of the line and sent into tents. Felt perfectly well until morning of December 31.

Present illness: That morning noticed vague muscular pains in anterior surfaces of thighs and in calfs, not well localized and dull in character. Also had a slight headache and felt giddy, though he noticed no physical weakness. At this time had no urinary symptoms, and thinks he had no fever. The next morning when he passed urine, noticed severe, burning, urethral pain. From that time on was troubled with severe urgency and frequency of urination (passing very small amounts as frequently as every half hour), burning pain throughout the act of micturition and profuse hematuria. Felt very depressed and the giddiness of the day before continued. The headache was gone but he had a spasmodic cough. "Carried on" until 5 p.m. when he was forced to stop. At that time temperature was 102.4° and pulse 120. Was taken to Field Ambulance and from there directly to the Casualty Clearing Station. At 5 a.m. on January 2, temperature was 102°. Then complained of extreme thirst, although he was nauseated by the very sight of food, and had severe pain just to the right of the sternum, increased by deep breathing.

At no time did he have any pain in the back. The blood in the urine was always well mixed in the specimen, and grossly visible. The pain persisted throughout the act of micturition, but was unassociated with tenesmus. The urine showed gross blood up to the time of his admission to this hospital. The major part of the dysuria ceased the next day, and the frequency of urination diminished steadily.

Physical examination on admission: Appears anemic. Slight hyperpnea. No edema. Tongue red and inclined to dryness. Throat congested. Tonsils enlarged. Chest: expansion good; no areas of dulness; breath sounds over right upper anterior chest a little increased and rough; many fine, crackling râles brought out by coughing over this area, from just below the clavicle to the 4th rib. Heart: no enlargement; action somewhat rapid, but regular; no murmurs. Pulse regular in force and rhythm; arterial tension does not seem increased. Abdomen entirely negative. No costovertebral tenderness. Knee jerks normal. Tenderness present over the shins and in the left calf. Urine dark red.

January 6. Three sputum examinations for tubercle bacilli have been negative.

January 7. Predominant organism in sputum is a lanceolate diplococcus, probably pneumococcus.

January 8. Dysuria and hematuria have both ceased and frequency is much less marked. Last night voided three times. Cough also improved.

Physical examination: Looks chronically ill, but is suffering no pain. Slight productive cough with muco-purulent sputum. Skin and mucous membranes pale, but clear. Tonsils not enlarged or red. Pharynx rather granular in appearance. No enlargement of lymph nodes. Chest: respiratory movements normal and equal in rate and depth; over the whole right upper lobe some dulness, with harsh breathing, voice and whisper, and subcrepitant and mucous râles, not cleared by coughing. Heart: examination as on January 1, except for blowing, systolic murmur, maximum over 2d right interspace, heard also over 2d left interspace and at apex, but not transmitted to the left. Pulse 54, regular, of good quality. Arteries soft.

Blood pressure: systolic, 120; diastolic, 78.

Abdomen: liver and spleen not felt. No areas of tenderness or hyperesthesia anywhere.

Ophthalmoscopic examination: Entirely negative.

Cystoscopic examination: Bladder urine clear. Mucosa normal, except over distal half of trigone and along upper border of trigone, where there are several relatively fresh hemorrhages. There are also two small ones, one just at the outer side of each ureteral orifice; and a fading group higher up on the bladder wall, on the left side. Urine culture sterile.

Specimens of hemorrhages in bladder mucosa removed with punch.

Kidneys not palpable. External genitalia, prostate and seminal vesicles normal.

Blood count: R. B. C. 2,700,000; hemoglobin 60 per cent. W. B. C. 10,780; p. m. n. 83 per cent; lymphocytes 17 per cent.

January 11. Cough much less severe. Dulness and harsh breathing still persist over right upper lobe, but râles are less numerous. Dysuria now diminished to a little discomfort on urination. Appetite good. Phenolsulphonphthalein, 35 per cent.

January 12. Frequency still diminishing: voided only twice last night.

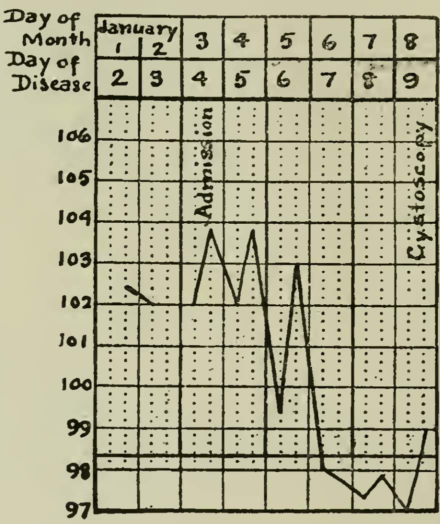
January 13. Cough almost gone. Chest signs clearing, no râles today.

January 15. Ophthalmoscopic examination still entirely negative. Patient now has to get up only once at night to urinate, and has practically no discomfort.

January 22. All signs in chest cleared up.

January 27. Discharged. Has been up and out for some time, much improved, with recovered strength. Lungs perfectly clear. Still has to get up once at night to urinate and is still conscious of very light discomfort in regions of bladder and urethra when he passes urine.

Phenolsulphonphthalein, 40 per cent.



CASE 12

Pathologic report of specimen of bladder mucosa (Capt. Pappenheimer): Sections show a small portion of bladder covered by a rather thin, but otherwise normal squamous epithelium. Underlying tissue edematous. Capillaries and venules dilated and engorged with blood. An irregular extravasation of blood into the loose cellular tissue. Inflammatory changes are found in none of the sections.

February 27. Report from patient in England: Urine, February 3, "negative quantitatively." Allowed up February 5. After going into town became very tired and short of breath. Pulse rate rose to 140, with precordial pain and uneasiness. No definite murmur and no pulse irregularity. Pulse remained irritable and cardiac symptoms continued for ten days, gradually improving with rest.

From that time on till date of note, has been fit except for recurrence of similar symptoms about once a week. Urine on four examinations during this period has shown no albumin, but always a few granular casts.

No temperature record obtained.

Urine examinations

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
January 1.....			"Blood present"		From Casualty Clearing Station
January 4.....		+	0	0	Many
January 8.....		0	0	0	0
January 9.....		0	0	0	0
January 11.....	1010	0	0	0	0
January 15.....	1015	0	0	0	0
January 22.....		0	0	0	0
February 3.....		0	0	0	Report of patient from England
February 27....		0			Few granular casts constantly Report of patient from England

Case XIII

Age twenty-two years. Labor corps. Total service one year and six months. Field service ten months.

Admitted: February 3, 1918.

Diagnosis on admission: Pyrexia of unknown origin.

Past history: Occupation in civil life that of driver in colliery. In France has worked in the front area, but has never been in the trenches. Was placed in labor corps because of absence of left eye, due to traumatic injury in childhood.

Present illness: Began January 29, with headache and severe pains in the back. Was sent at once to Casualty Clearing Station. That evening noticed burning on urination and blood in his urine. No frequency or urgency. No dyspnea or edema.

Symptoms subsided rapidly in Casualty Clearing Station.

Physical examination on admission: Still complains of slight pain in the small of the back. Does not appear acutely ill, but is somewhat pale and thin. Left eye gone. Teeth in poor condition. Skin and

mucous membranes clear. No edema or hyperpnea. Lungs clear. Heart: Not enlarged; sounds of good quality; no murmurs or accentuations. Pulse 60, regular. Blood pressure; systolic 148; diastolic 80. Arteries soft. Abdomen negative except for slight tenderness in right hypochondium and right costovertebral angle.

February 5. Cystoscopic examination: Posterior wall and posterior parts of both lateral walls reveal many areas of relatively fresh hemorrhage in the bladder mucosa. These tend to be grouped and are mostly proximal to the trigone. Several small hemorrhages occur about, but not immediately adjacent to, the right ureteral orifice. Both ureteral opening are normal. Some groups are large and blotchy, while others seem to consist of aggregations of minute hemorrhages. Rest of bladder wall normal. No signs of inflammation anywhere. Two specimens removed with cystoscopic punch.

Catheterized specimen of urine (5 cc.) injected subcutaneously into male guinea pig. Pig killed after ten days. Autopsy revealed normal organs. Sections of liver, kidneys, bladder, lungs and other organs showed no organisms by Levaditi or ordinary stains. Culture of same specimen showed only contaminating staphylococci in one plate.

External genitalia, prostate and seminal vesicles normal. Kidneys not felt.

February 6. Ophthalmoscopic examination negative.

February 7. Complains of pains in left anterior chest. Heart and lungs negative.

February 8. Phenolsulphonphthalein, 40 per cent.

Blood culture sterile. Blood count: W.B.C. 9600; p.m.n. 57 per cent; lymphocytes 43 per cent.

February 9. Endoscopic examination. Instrument entered posterior urethra only with considerable pressure because of resistance of patient. One red spot found on right side of floor of posterior urethra, thought to be due to traumatism. Urethral mucosa otherwise normal.

February 11. Feels all right. Still looks somewhat pale and debilitated.

February 16. Phenolsulphonphthalein, 43 per cent.

February 18. Cystoscopic examination: Large area, diffusely red, composed apparently of almost completely faded hemorrhages, on right posterior wall, and smaller similar area on left side, nearer prostatic border. Remainder of mucosa seems entirely normal. Specimen removed with cystoscopic punch.

February 19. This morning pain in suprapubic region, right lower abdomen and right side of back. No pain on urination. Some tenderness in right lumbar region, both in front and behind, and some tenderness also in right iliac region. No masses felt.

February 22. Last night and today, pains shooting down right thigh and leg. Pains in back gone.

February 24. Blood count: W.B.C. 12,300; p.m.n. 61 per cent; lymphocytes 31 per cent; large mononuclears 5 per cent; transitionals 2 per cent; eosinophiles 1 per cent.

February 27. Phenolsulphonphthalein, 40 per cent.

March 4. Symptoms gone.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
February 4	+++	+	0	Few red blood cell casts
February 5	++	++	+	0
February 8	+	+	++	Granular and cellular
February 11	++	++	+	Few hyaline
February 19	++	+++	++	Many hyaline and red blood cell casts
February 21	++	+	+++	Hyaline, granular and cellular
February 22		+	+++	Hyaline, granular and cellular
February 24	+	+++	++	Hyaline and granular
February 25	+	++	+++	0
February 26	++	+++	++	Hyaline, some with red cells in them
March 5	+	+	++	Hyaline, and fine and coarse granular
March 11	+	++	++	Hyaline and red blood cell casts
March 12	+	++	++	Finely granular
March 17	+	+	0	Hyaline, coarse and fine granular
March 20	+	++	0	Coarse granular casts

March 12. Last night and today attacks of lancinating pain in left costovertebral angle. No tenderness.

March 17. Complains of nausea.

March 19. Still slight pain on urination; no frequency. Pains in back gone.

March 24. Blood count; R.B.C. 4,850,000; hemoglobin 80 per cent; W.B.C. 8100; p.m.n. 58 per cent; lymphocytes 35 per cent; transitionals 1 per cent; eosinophiles 5 per cent; basophiles 1 per cent.

March 25. Phenolsulphonphthalein, 30 per cent. Patient evacuated to England.

Pathologic report (by Capt. Pappenheimer): *February 5.* Fragment of bladder wall: The epithelium is practically intact over the fragment.

The sub-epithelial tissue, under the high power, shows vaguely the outlines of red corpuscles in the stroma, almost completely decolorized. Deeper down there is edema with deposition of a granular coagulum between the collagen fibriles. There are no inflammatory changes. One of the veins contains what is apparently a cell-fragment thrombus, consisting of a mass of pink material in which are embedded numerous irregular nuclear fragments with a few intact wandering cells.

Specimen of February 18 shows similar picture.

Temperature. 102° January 29; 99.8° January 30. No other record before admission to hospital. While in hospital, elevations between 99° and 100° up to the time of discharge.

Case XIV

Age nineteen years. Infantryman. Total service twelve months. Field service three months.

Admitted: February 3, 1918.

Diagnosis on admission: Nephritis.

Past history: Butcher in civil life. In 1916 sick three weeks with blood poisoning. Since coming to France thinks he has lost weight and has been troubled with some shortness of breath on route marches, which has forced him to fall out twice.

Present illness: Caught cold about January 21 (aphonia and cough). January 30 noticed blood in his urine and severe terminal dysuria. Had to get up two or three times a night to pass urine and suffered also with diurnal frequency. Passed usually small amounts at each voiding. No headache, edema, or dyspnea; some dizziness. No temperature recorded at Casualty Clearing Station. Has not felt feverish. Hematuria, dysuria and frequency continued until admission to this Hospital. Also had slight suprapubic pain.

Physical examination on admission: Appears acutely ill. Color good. Skin and mucosa clear. No edema or hypernea. Lungs: scattered râles over both sides of chest, more marked at right apex. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse 60, regular. Blood pressure; systolic 122; diastolic 80. Arteries soft.

Abdomen negative except for moderate tenderness in suprapubic region and both costovertebral angles.

February 3. Blood count; R. B. C. 4,800,000; hemoglobin, 90 per cent; W.B.C. 6800; p.m.n. 64 per cent; lymphocytes 28 per cent; large mononuclears 7 per cent; eosinophiles 1 per cent.

February 5. Slight pain on urination.

Phenosulphonphthalein, 13 per cent.

Cystoscopic examination: Numerous groups of large hemorrhages, extending in horse-shoe form around posterior half of bladder, just above prostatic border. Some are nearly 1 cm. in diameter, often confluent and surrounded by minute hemorrhages. There are also a few small hemorrhages, along the border of the trigone. Remainder of bladder wall and ureteral orifices normal. No signs of inflammation about hemorrhages, or elsewhere. Two specimens removed with bladder punch.

Catheterized urine specimen (5 cc.) injected subcutaneously into male guinea-pig. After ten days, autopsy of pig revealed no pathologic lesions anywhere and no organisms were found in organs stained with Levaditi or ordinary stains.

Culture of urine sterile.

External genitalia, prostate and seminal vesicles normal. Kidneys not palpable; no tenderness.

February 7. Pain on urination has almost disappeared. No other symptoms.

February 8. Ophthalmoscopic examination negative.

February 9. *Endoscopic examination:* There is a small dark, blue, well defined hemorrhage on the top of the verumontanum, about 3 mm. in diameter. The remainder of the urethra is normal.

February 12. Blood pressure: systolic 132; diastolic 88.

Phenolsulphonphthalein, 17 per cent.

February 14. Blood pressure; systolic 142; diastolic 80. Blood count: W.B.C. 9000; p.m.n. 85 per cent; lymphocytes 9 per cent; transitionals 5 per cent; eosinophiles 1 per cent. Blood culture sterile.

February 18. Phenolsulphonphthalein, 27 per cent.

Cystoscopic examination: Group of 4 or 5 small hemorrhages on left wall, near prostatic border. One elongated, fading hemorrhage on right wall and one questionable one in the mid-line high up on the posterior wall. Rest of bladder mucosa normal. One specimen removed with bladder punch.

February 22. Phenolsulphonphthalein, 32 per cent.

February 28. Does not gain strength. Has slight headache and occasional dizziness. Phenolsulphonphthalein, 25 per cent.

March 4. Still complains of occasional headache.

March 6. Complains of toothache. Right lower jaw and submaxillary lymph nodes swollen and tender. Four decayed molar stumps removed and abscess drained.

March 9. Swelling of jaw and adjacent lymph nodes practically disappeared.

March 12. Phenolsulphonphthalein, 48 per cent.

March 17. Complains of dysuria. No frequency. Urine bloody.

March 18. Still has dysuria. Urine no longer grossly bloody, but appears smoky.

March 23. *Cystoscopic examination:* On posterior part of left wall, less than a centimeter from the prostatic border is an elevated, irregular, dark red nodule, giving the impression of a superficial hemorrhage elevating the mucosa. Just above this is a tiny flat hemorrhage in the line of a small vessel. A similar one is seen on the right side of the trigone. Remainder of bladder wall and ureteral orifices normal. Larger hemorrhage removed with punch.

March 25. Phenolsulphonphthalein, 55 per cent.

March 29. Complains of some nausea and giddiness today. Slight frequency and dysuria.

April 2. Last night and this morning vomited several times. Complains of headache and very slight terminal dysuria. Patient evacuated to England.

Pathologic report: (by Captain Pappenheimer):

February 5. Section consists of a 2 mm. sized fragment of bladder wall, covered on three sides by intact epithelium. Here and there this is being penetrated by a few mononuclear wandering cells. The submucous tissue is edematous. The nuclei of the connective tissue cells are curiously distorted and in some areas there is marked karyorrhexis. Some of the small arterioles contain pink-staining thrombotic masses, in which are embedded a few nuclear fragments. These can be followed through a number of sections. There are many wide endothelial-lined spaces, possibly dilated lymphatics. Some of these show a loose round-celled infiltration about them. One of the largest arteries in the section contains what is apparently a plug of organized tissue, overgrown by endothelium. In certain sections there is definite hemorrhage (with broken down red blood cells) into the loose cellular tissue, extending in some places to the epithelium.

February 18. Small fragment of bladder wall: the epithelium over one portion of the fragment is reduced to a single flattened layer of cells. The subjacent tissue is the seat of a fairly recent hemorrhage. There is a considerable amount of hemosiderin, both extra- and intracellular. There is edema in the remaining portion of the stroma. There are no large arterioles in the section.

March 23. Small fragments of bladder wall: the epithelium is desquamated over a portion of the fragment, probably an artifact. There are traces of an old hemorrhage in the connective tissue. The ghosts of the corpuscles are still to be seen and there is an abundance of hemosiderin pigment, chiefly extracellular. The nuclei of the connective tissue cells are much distorted and pyknotic. No inflammatory changes nor vascular lesions.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
February 4....	+++	++	++	0
February 5....	++	++	+	Cellular and hyaline
February 14....	++	"Smoky"	0	Many red blood cell casts
February 24....	++	++	++	Hyaline and cellular
February 26....	+	+	+	Hyaline, granular and red blood cell casts
February 27....	++	+	0	Hyaline casts filled with red blood cells
March 5.......	+	+	+	Finely granular and cellular
March 11.......	+	+++	0	Hyaline and red blood cell casts
March 17.......	++++	++	0	Granular, hyaline and red blood casts
March 18.......		"Smoky"		
March 20.......	+++	+++	+++	Hyaline and red blood cell casts
April 2.........	+++	++	++	Many hyaline and coarse and fine granular

Temperature: No records before admission to Hospital. While in hopital occasional elevations of 100° or 101° No rise with recurrence of symptoms and bladder hemorrhages on March 17.

Case XV

Age thirty years. Labor corps. Total service three and one half years. Field servce five months.

Admitted: February 17, 1918.

Diagnosis on admission: Acute nephritis.

Past history: Rheumatic fever in 1915, when on the Mediterranean front (symptoms pain, without swelling, in all his joints). Was in the hospital from this and "shell shock" from December 1915, to September 1916. At the end of that time was "boarded" and sent into a labor company. Has had slight shortness of breath on exertion since childhood.

Present illness: Began February 6, with frequency of urination (passing only small amounts at each voiding). Voided about ten times during the day and four times at night.

In the morning of February 8 was seized with severe headache and giddiness. In the afternoon noticed that his urine was bright red, and had initial dysuria. Frequency continued unchanged. Reported sick the next day and was put on light duty.

February 11. Sent to Casualty Clearing Station where he was found to have blood and albumin in his urine and puffiness of the face, but no oliguria. On admission to this hospital frequency diminished, but he still has to get up three times at night. Gross hematuria stopped on the 15th. Says he has had sharp attacks of pain in both sides of the back at intervals since onset.

Physical examination on admission: Appears chronically ill and pale. Rather poorly developed. Skin pasty; no edema or hemorrhages. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse 72, regular. Blood pressure: systolic, 148; diastolic, 80. Lungs and abdomen negative. No tenderness in loins.

February 18. Phenolsulphonphthalein, 44 per cent.

Ophthalmoscopic examination negative.

Cystoscopic examination: Two hemorrhages about the right ureteral orifice and a small group posterior and median to these. Remainder of bladder wall normal. Specimen removed with punch.

External genitalia, prostate and seminal vesicles normal.

Catheterized specimen of urine cultured: no growth; 4 cc. injected subcutaneously into male guinea-pig. Pig returned to stock March 8, was under observation and without symptoms May 24.

February 27. Endoscopic examination: Only imperfect view obtained because of small size of urethra, but no urethral lesions discovered.

March 5. Blood count: Hemoglobin 77 per cent; R.B.C 4,770,000; W.B.C. 7700; p.m.n. 58 per cent; lymphocytes 39 per cent; eosinophiles 3 per cent. Slight poikilocytosis and central pallor of red cells.

March 9. Still has to get up once every night to urinate. Pallor and pasty look and general debility continue.

March 12. Phenolsulphonphthalein, 35 per cent.

March 19. Nycturia continues unchanged. No pains. No dysuria.

March 24. Blood count: Hemoglobin, 75 per cent; R. B. C., 4,500,000; W. B. C., 6000; p.m.n., 46 per cent; lymphocytes, 49 per cent; eosinophiles, 4 per cent; basophiles, 1 per cent.

March 25. Phenolsulphonphthalein, 40 per cent.

Patient evacuated to England.

Pathologic report (by Captain Pappenheimer):

February 18. Small fragment of bladder mucosa: epithelium is continuous over the entire fragment, except over a small pedicle-like tongue of connective tissue. There is extreme dilatation of all capillaries, with a recent hemorrhage into the subepithelial tissue. No inflammatory changes or vascular lesions.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
February 11....	"Small quantity"	"Blood present"		Report from Casualty Clearing Station
February 13....	"Trace"	"Tinge"		Report from Casualty Clearing Station
February 14....	"Trace"	"Blood gone"		Report from Casualty Clearing Station
February 18....	++	++	+	Occasional hyaline
February 21....	++	+++	++	Hyaline, granular and red blood cell casts
February 24....	+	+	+	Hyaline and red blood cell casts
February 25....	++	+++	+	Hyaline
March 5.......	+	+	0	Finely granular and hyaline
March 11.......	+	+	++	Hyaline, finely granular and cellular
March 20.......	+	+	+	Hyaline and finely granular

Temperature: No records before admission to hospital. Irregular temperature of 100° to 101° until February 25. After this occasional rises to 99° or 100° until March 18.

Case XVI

Age twenty-three years. Cycle battalion. Total service two years and four months. Field service twelve months.

Admitted: March 1, 1918.

Diagnosis on admission: Nephritis.

Past history: Entirely negative.

Present illness: Began February 12 with hematuria, frequency of urination (passing small amounts every hour during the day and six or seven times a night), burning pain on urination and urgency. Slight cough. No headache. Slight swelling in both hands, but no other edema. No giddiness or weakness. Admitted to Stationary Hospital February 17, where he was found to have albuminuria. Improved rapidly.

On admission to this hospital, frequency greatly diminished (only has to get up once at night); hematuria and dysuria gone. Complains of some pain in the small of the back, not radiating, which has developed since February 17.

Physical examination on admission: Does not appear ill. No edema or hyperpnea. Skin and mucous membranes entirely clear and of good color. Heart: apex impulse in the 5th space, 1 cm. to the left of the nipple line; dulness extends from the right border of the sternum to a point 2 cm. to the left of the left nipple line; soft blowing, systolic murmur at apex, not transmitted; no accentuations. Pulse 72, regular. Blood pressure: systolic, 116; diastolic, 82. Artery walls soft. Lungs clear except for slight relative dulness at extreme right base behind. Abdomen negative. No tenderness in loins.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
February 21....	"Fair amount"			Report from Stationary Hospital
February 27....	"Trace"			Report from Stationary Hospital
March 2.......	+	0	0	0
March 4.......	+	0	0	Few hyaline
March 8.......	++	++	+	Frequent red blood cell casts
March 11.......	++	+++	+	Hyaline, finely granular and red blood cell casts
March 20.......	++	0	0	Finely granular

March 2. Cystoscopic examination: Two confluent, light red patches, apparently old hemorrhages, in the paths of the small vessels on the inner side of the right ureteral ridge, just above the ureteral orifice. Remainder of bladder wall normal. Specimen removed with punch. External genitalia and seminal vesicles normal. Prostate slightly boggy and nodular about the outer border, but not indurated or enlarged. Kidneys cannot be felt.

March 4. Ophthalmoscopic examination negative. Phenolsulphonphthalein, 33 per cent.

March 9. Still has to urinate about three times a night.

March 24. Slight headache. Phenolsulphonphthalein, 48 per cent. Evacuated to England.

Pathologic report (by Captain Pappenheimer):

March 2. Small fragment of bladder mucosa: the epithelium appears intact throughout. The connective tissue is edematous and contains large pigment-bearing phagocytes. There is no definite hemorrhage. No inflammatory changes or vascular lesions.

Temperature: No records before admission to hospital. Temperature never above 99° while in hospital.

Case XVII

Age twenty-nine years. Infantryman. Total service eight years. Field service five months.

Admitted: March 11, 1918.

Diagnosis on admission: Nephritis.

Past history: Frequent colds and bronchitis in childhood and youth. For about eight years slight cough and expectoration. No pleurisy or hemoptysis. Some shortness of breath on exertion. Five years ago diphtheria, without complications. Was rejected for the army in 1915 because of pulmonary conditions and varicocele. Has always had to get up once or twice at night to urinate.

Present illness: Began about February 24, after he had been in the trenches about four days, with general weakness and an exacerbation of his cough. On March 3, he was seized with general pains and giddiness and suddenly fainted in his dugout. Next day noticed blood in his urine and pain in the lower abdomen at the end of urination, associated with urgency and frequency. The hematuria stopped after about three days, but the dysuria and frequency lasted a few days longer. Since then he has improved, but continues to have general pains, especially in the back and legs. No dyspnea or edema. Thinks his temperature was 104° on March 5.

Note of March 9 from Casualty Clearing Station gives temperature 99°.

Physical examination on admission: Does not appear acutely ill. Somewhat pale. Skin and mucous membranes clear. No hyperpnea or edema. Finger nails slightly curved, suggestive "clubbing."

Lungs: breathing rather high pitched over left upper lobe, diminished in both lower axillae and especially the left lower lobe behind, where there are also fine, moist râles. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse 72, regular. Blood pressure: systolic, 122; diastolic, 66. Arteries soft. Abdomen negative. Some tenderness in both costovertebral angles and along both shins.

March 12. Still complains of pains in legs, back and shoulders. Phenolsulphonphthalein, 35 per cent.

March 13. Pains in back and shoulders continue; none in legs.

Cystoscopic examination: Two small spots in course of vessel just below and internal to right ureteral orifice, probably very minute hemorrhages. Remainder of bladder wall entirely normal.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
March 9.......	"Trace"	"No blood"		Report from Casualty Clearing Station
March 11.......	++	++	0	Many hyaline and red blood cell casts
March 12.......	++	+	+	Red blood cell casts
March 20.......	++	+	+	Red blood cell casts
March 23.......	+	++	++	Hyaline, coarsely granular and cellular

March 19. Been up two days. Has occasional pains at night. No nycturia.

March 23. Cystoscopic examination: Bladder mucosa and ureteral orifices entirely normal. Spots noticed before, no longer visible.

March 25. Complains of severe headache over the eyes. Blood pressure: systolic, 108; diastolic, 72.

No paralysis or alteration of reflexes.

Ophthalmoscopic examination negative.

Phenolsulphonphthalein, 70 per cent.

Headache disappeared after free catharsis.

April 4. No râles in chest today. Otherwise signs unchanged. General symptoms greatly improved. No urinary symptoms. Evacuated to England.

Temperature. No records before admission to hospital. Three rises to 100° to 101° while in hospital; the last on March 30.

Case XVIII

Age twenty years. Infantryman. Total service one year. Field service eight months.

Admitted: June 13, 1918.

Diagnosis on admission: Inflammation of bladder.

Past history: Was a plumber in civil life. Has been subject to periodic headaches. Measles December, 1917. Was buried by shell a few weeks before admission to hospital.

Present illness: Seven weeks before admission to hospital had pains in legs, head and back, and in bladder region, accompanied by frequency of urination and scalding. Urine was red. Did not report sick and symptoms passed off in two days, leaving him with tired, drowsy feeling.

Five days before admission, sudden recurrence of similar pains, hematuria and dysuria.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
	+++	+++	+	Several hyaline and granular
June 28.........	+++			Few granular
July 3.........	++++	++		Several red blood cells and hyaline casts

Physical examination on admission: Complains of headache, pains in back and legs and slight frequency. Appears well nourished. Color good. Tongue coated. Teeth very bad. No hyperpnea or edema. No signs of hemorrhages in skin or visible mucous membranes. Lungs clear. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse normal in rate and rhythm. Blood pressure: systolic, 135; diastolic, 85. Abdomen: tenderness over bladder region; kidneys neither tender nor palpable.

June 18. Radiograph shows no evidence of urinary calculus.

June 22. Cystoscopic examination: Bladder mucosa normal except for patch of seven or eight fading hemorrhages on posterior wall well above trigone. Ureteral catheterization: urines from bladder and from both ureters show moderate number of red blood cells and many blood casts, but no leucocytes.

June 27. Complains of pain in back. Gets up once a night to urinate.

June 30. Pain in bladder region.

July 5. Severe pains in legs last night. No tenderness. Slight diarrhea (six movements during day). No blood in stools.

July 7. Diarrhea has ceased. Pain in bladder region persists. Has had almost constant headache since admission.

Phenolsulphonphthalein, 50 per cent.

No note on temperature in records.

Case XIX

Age twenty-one years. Labor company. Total service three years. Field service twenty-three months.

Admitted: July 9, 1918.

Diagnosis on admission: Hematuria.

Past history: Was in infantry prior to attack of trench fever in May, 1917. Then in hospital three months. Subsequently in hospital twice for weakness, shortness of breath and pain on exertion in left chest.

Present illness: Began July 5 with headache and pains in right costovertebral region. The latter were dull and steady with occasional lancinating exacerbations. Next day had gross hematuria and terminal dysuria and extreme frequency (about every half hour at night). Vomited three times. Noted slight pain in left side of back as well as right.

At the Casualty Clearing Station July 8, diagnosis influenza with hematuria. Temperature 99°.

Gross hematuria still present July 9. Pains in back considerably diminished, but dysuria persists.

Physical examination on admission: Appears acutely ill and somewhat debilitated. Has slight, dry cough. No hyperpnea or edema. No signs of hemorrhages in skin or visible mucous membranes. Lungs clear. Heart: not enlarged; sounds of good quality; no murmurs or accentuations. Pulse regular, not rapid. Blood pressure: systolic, 110; diastolic, 80. Abdomen: marked tenderness in both hypochondria and both lumbar regions, with hyperesthesia. Right kidney barely palpable.

July 11. Cystoscopic examination: There are three groups of hemorrhagic spots on left, posterior lateral wall. Each group is a conglomerate, irregular mass, surrounded by small hemorrhages, some definitely fading. The largest group contains 30 to 40 hemorrhages. Proximal to these patches is a long area of congestion, fairly well

localized. There are two irregular, hemorrhagic splotches on right postero-lateral wall, near prostatic border, one on the trigone in the mid-line, and two groups higher on the posterior wall. There is marked congestion about the areas on the posterior wall. Remainder of bladder wall and ureteral orifices quite normal.

Urine culture: no growth on aerobic and anaerobic media (urine smoky with reddish tinge).

Blood culture sterile.

July 12. Complains pain in right flank. Right kidney slightly tender and possibly enlarged.

July 15. Right kidney still palpable, but not tender. Frequency persists (three times a night), without dysuria.

July 16. Only occasional slight pain in right flank.

Urethroscopic examination: On left side of verumontanum is a well defined hemorrhagic spot, and another at about the usual site of the utricle (not identified).

July 17. Much improved. No pains.

July 21. Pain in left side of back with tenderness in left costo-vertebral angle. Slight tenderness over palpable right kidney and in suprapublic region. Frequency continues unchanged. No dysuria. Heart and lungs negative.

Evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 9.........		"Obvious blood"		
July 9.........	+++	++++	0	Several granular and hyaline
July 13.........	0	0	+	Few granular
July 19.........	+	+	+	Occasional granular and hyaline
July 22.........	+	+	0	Few granular and cellular

Temperature: Frequently 99° by mouth, and never above 99.4°.

Case XX

Age twenty years. Engineer signal corps. Total service two and one-half years. Field service thirteen months.

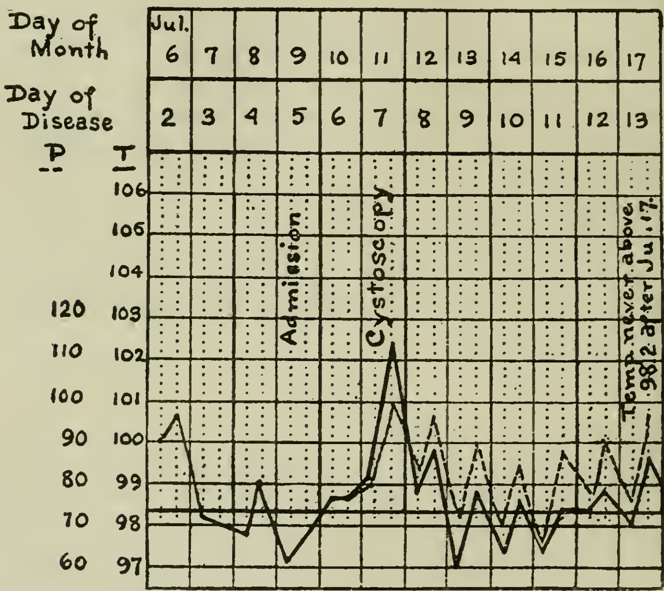
Admitted: July 9, 1918.

Diagnosis on admission: Nephritis.

Past history: In civil life worked in cotton-mill. Pneumonia at age of eleven. In hospital about two weeks with trench fever, six months ago.

Present illness: Began July 5, with headache, herpes labialis, hematuria and frequency of urination (four or five times during the night). Next day frequency ceased but hematuria continued. Noticed pain in lower abdomen during urination.

Physical examination on admission: Appears acutely ill. Somewhat pale. Slight, dry cough. No hyperpnea or edema. Marked herpes



Case 20

about both corners of mouth. No signs of hemorrhages in skin or visible mucous membranes. Lungs: few fine râles at left base posteriorly after coughing. Heart: not enlarged; no murmurs or accentuations. Pulse regular, normal rate. Blood pressure: systolic, 128; diastolic, 62. Abdomen: spleen palpable 1 cm. below costal margin; liver and kidneys not felt; marked tenderness in both hypochrondria and in right lumbar region.

July 11. Cystoscopic examination: Bladder mucosa normal excepting one group of six fading hemorrhages, high on posterior part of left wall. Ureteral orifices normal.

Urine culture shows, after forty-eight hours, a Gram-positive streptococcus and a smaller Gram-negative bacillus, forming gas on anaerobic media. Subcultures show aerobic hemolytic streptococcus. (Urine smoky and slightly blood-tinged.)

Blood culture sterile.

July 12. Headache and severe pains in legs and back last night, with temperature 102.4°. Lungs clear.

July 13. Headache gone. Pain across sacrum and in thighs.

July 15. Feels well. Spleen still palpable. Some frequency (twice a night) and slight terminal dysuria. No history of malaria or tropical residence.

July 16. Urine culture sterile.

July 18. Some pain in back and legs and headache. Frequency unchanged. Spleen still palpable.

July 21. Pains and frequency persist. Spleen no longer palpable.

July 22. Evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 6.........	"Present"	"Blood stained"		
July 9.........	+++	0	0	Few hyaline
July 14.........	++	+	+	Few red blood cell and white blood cell casts
July 19.........	+	+	+	Moderate number of granular and cellular

Case XXI

Age forty years. Infantryman. Total service seventeen months. Field service seven months.

Admitted: July 10, 1918.

Diagnosis on admission: Influenza.

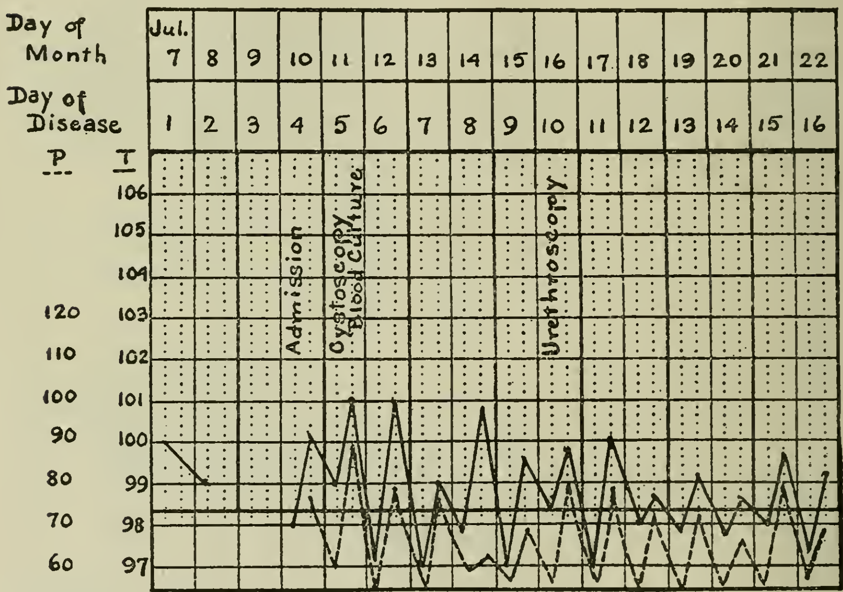
Past history: Not obtained.

Present illness: Began July 7 with headache, cough and pains in shins. Two days later frequency (four times a night), dysuria and hematuria. Also had chilly sensations and dizziness.

Physical examination on admission: Dysuria and frequency persist. Has considerable cough and headache. No edema or hyperpnea. No signs of hemorrhages in skin or visible mucous membranes. Lungs:

many musical râles. Heart: not enlarged; faint systolic murmur at apex; no accentuations. Abdomen negative. Marked tenderness in both shins.

July 11. Cystoscopic examination: On right half of posterior bladder wall, well above trigone is an area of conglomerate hemorrhages about 2 cm. in diameter. On posterior part of left lateral wall is an elongated patch of well defined hemorrhages which extends through an area of faint hemorrhages to a group of more distinct hemorrhages on the left half of the anterior wall. Remainder of bladder wall seems quite normal.



CASE 21

Urine blood-stained and smoky.

Right ear shows herpetic lesion involving whole auricle.

Blood culture sterile.

July 15. Complains of anorexia and pains in ears and tinnitus. Headache and shin pains have ceased. Dysuria and frequency diminished (twice a night).

July 16. Urethroscopic examination: One hemorrhage 2–3 mm. in diameter found on anterior declivity of verumontanum. Rest of posterior urethra normal.

July 22. Some pains in shins with very little tenderness. Dysuria has ceased, but frequency persists (twice a night).

Evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 11.........	++++			Many hyaline and granular
July 12.........	++++	0	0	Many granular
July 14.........	++	+	+	Many granular and cellular
July 19.........	+++	+	+	Moderate number of granular and cellular

Case XXII

Age twenty-two years. Driver. Total service thirty-four months. Field service seven months.

Admitted: July 10, 1918.

Diagnosis on admission: Nephritis.

Past history: Tonsillitis twice. Rejected for army early in the war because of deafness.

Present illness: Began about a week before admission with headache, weakness and anorexia. Three days later noticed hematuria and frequency (two or three times a night), but no dysuria. Slight diarrhea at onset. Gross hematuria ceased July 6. Has had shooting pains across lower part of back.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 11.........	++			Several hyaline
July 14.........	0	+	+	Few red and white blood cell casts
July 19.........	0	+	+	Occasional granular

Physical examination on admission: Appears moderately ill. Skin and mucous membranes clear. No edema or hyperpnea. Lungs clear. Heart: area of dulness extends 13 cm. to the left and 4 cm. to the right of the mid-line; no murmurs or accentuations. Pulse regular, rate normal. Blood pressure: systolic, 150; diastolic, 78. Abdomen: slight tenderness in both lumbar regions.

July 11. Urine smoky.

Cystoscopic examination: High up on posterior part of right lateral wall is a triangular hemorrhagic spot, surrounded by a small network of vessels, two of which definitely end in hemorrhages. Remainder of bladder and ureteral orifices normal.

July 16. Still slight headache.

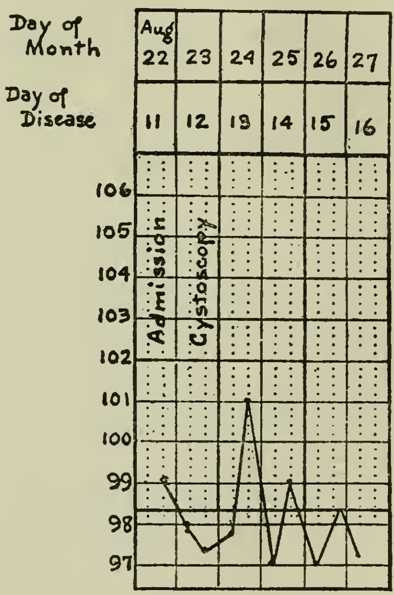
July 17. Dysuria has appeared, without frequency or hematuria.

July 20. Transferred to hospital for skin diseases for scabies.

Temperature has never been recorded above 99° by mouth.

Case XXIII

Age twenty-one years. Infantryman. Total service thirty-eight months. Field service nine months.



Case 23

Admitted: August 22, 1918.

Diagnosis on admission: Hematuria.

Past history: Six years ago attack of pains in knees, ankles and back, without swelling of joints. In 1916 or 1917, while in the army, had precordial pain and exertional dyspnea; diagnosis of cardiac valvular

disease and dilatation was made. Still has pain on exertion, but can do all but very heavy duties.

Present illness: Began August 12 with hematuria and dysuria. Felt feverish. Later severe headache and pains in back, knees and ankles.

Radiography at Casualty Clearing Station revealed no urinary calculus.

Physical examination on admission: Appears well nourished, with good color. Skin and visible mucous membranes clear. No edema or hyperpnea. Lungs clear. Heart: not enlarged; no murmurs; second sound everywhere ringing in character. Pulse regular. Rate normal. Blood pressure: systolic, 128; diastolic, 80. Abdomen: slight tenderness in both hypochondria; kidneys not felt.

August 23. Cystoscopic examination: Two or three small, fading hemorrhages in the course of vessels on the posterior wall. Remainder of bladder wall normal.

Urine culture: Sterile (urine blood-tinged). Smears negative.

August 27. Still has pain in back. No tenderness.

Evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 17.......	"Present"	"Present"		Urine smoky
August 23.......	+++	+++	+++	Many granular

Case XXIV

Age nineteen years. Infantryman. Total service nine months. Field service three months.

Admitted: August 28, 1918.

Diagnosis on admission: Hematuria.

Past history: Scarlet fever in infancy. Has had precordial pain and slight shortness of breath at intervals.

Present illness: Began August 20 with diarrhea. Three days later malaise, but diarrhea had ceased. Next morning noticed hematuria and pains in back, legs and chest. Hematuria ceased August 27.

Physical examination on admission: Complains of dysuria and general weakness. Appears acutely ill. Color good. Skin and mucous membranes clear. No edema or hyperpnea. Lungs clear. Heart: not enlarged; no murmurs or accentuations. Abdomen: tenderness in left hypochondrium and both lumbar regions.

August 30: Severe pain and tenderness over sacrum and in flanks. No tenderness in costo-vertebral angles. Still dysuria and frequency (three times a night).

September 1. Cystoscopic examination: On right bladder wall is a confluent hemorrhagic patch about 2 by 0.5 cm. and there is a similar area on posterior wall just above left ureteral orifice. One small, fading group of hemorrhages on left anterior wall. Remainder of bladder wall normal.

Evacuated to England.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 28	+	+++	+	Hyaline, granular and red blood cell casts present

Temperature: No records before admission to this hospital. 100.8° August 30. Otherwise normal.

Case XXV[5]

Age twenty-one years. Infantryman. Total service two and one-half years.

Admitted: Date unknown.

Diagnosis on admission: Gas poisoning.

Past History: Gonorrhea one year ago. Was well until present illness.

Present illness: Poisoned by shell gas in July, 1918. At that time thinks he passed blood in urine for one day only. At Base Hospital improved and was placed on "work detail." The morning of October 27 noticed hematuria and frequency of urination, associated with general malaise.

October 29. Voiding small amounts of bloody urine every forty-five minutes, with considerable dysuria.

Physical examination: Appeared moderately ill. No edema or hyperpnea. No signs of hemorrhages in skin or visible mucous membranes. Lungs and heart normal. Abdomen: negative. External genitalia, prostate and seminal vesicles normal.

[5] Case seen by one of us in consultation at a Base Hospital in the American Expeditionary Force.

Urine: Albumen + + + +. Macroscopic blood. Epithelial and red blood cell casts.

Blood count: W. B. C. 7200; 50 per cent small mononuclears.

Phenolsulphonphthalein, 27 per cent on two successive days.

October 30. Urine smoky.

Cystoscopic examination: Five to six small hemorrhages to the inner side of the left ureteral orifice, and another group in the midline, just above the trigone. Remainder of mucosa and ureteral orifices normal.

Temperature: Reached 102°, October 28; 101°, October 29; 101.5°, October 30.

Case XXVI

Age forty-five. Infantryman. Total service nineteen months. Field service thirteen months.

Admitted: July 13, 1917.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
Jnly 7.........	"Albumin present"	"Blood present"		Granular (Casualty Clearing Station)
July 13.........	+++	+	+	Present

Diagnosis on admission: Hematuria.

Past history: Scarlet fever in childhood. Rheumatic fever nine years ago and five years ago. Was refused life insurance three years ago for heart disease. Has had dyspnea on exertion at intervals for years, but has been able to "carry on" without any difficulty.

Present illness: Began July 7, while in trenches, with headache, pains in shins, slight chills, temperature, hematuria and frequency of urination. No edema.

Physical examination on admission: No hyperpnea or edema. Skin and mucous membranes clear. Heart: somewhat enlarged to the left and downwards, with a systolic murmur at the apex, but no accentuations. Pulse 72, regular. Blood pressure: systolic 110; diastolic 78. Lungs: slight signs of emphysema. Abdomen negative. No tenderness made out. Cystoscopy not done and patient evacuated to England.

Temperature: 101.8° July 9; returned to normal July 11.

Case XXVII

Age twenty years. Infantryman. Total service one year. Field service six months.

Admitted: March 11, 1918.

Diagnosis on admission: Nephritis.

Past history: "Heart disease" three years ago (pains in heart and shortness of breath). Since then has been short of breath on exertion (after running only twenty yards) and has always had to drop out on route marches. Was never rejected for the army. Was a miner in civil life.

Present illness: Began February 27, with pains in back, abdomen and legs, headache, dizziness, swelling of the face, shortness of breath on the least exertion and pain in the back during urination. Urine contained blood.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
March 4.....	"Fairly large amount"	"Blood present"		Casualty Clearing Station
March 6.....	"Albumin +"	"Still some blood"		Casualty Clearing Station
March 12.....	+++	++	++	Hyaline, finely granular, and a great many red blood cell casts

Physical examination on admission: Does not look acutely ill. No edema. Respiration rather rapid and superficial. Heart: not enlarged; no murmurs; pulmonic second sound somewhat accentuated. Pulse 90, regular. Blood pressure: systolic 140; diastolic 96. Lungs: slight dulness over right upper lobe with a few subcrepitant râles at right apex, behind. Abdomen negative.

March 12. Considerable pain in legs and arms.

Patient evacuated to England without cystoscopy.

Temperature: No records except March 7 when temperature was 100°.

Case XXVIII

Age twenty-six years. Infantryman. Total service fourteen months. Field service eight months.

Admitted: August 21, 1917.

Diagnosis on admission: "Nephritis." (?)

Past history: Was told he had "kidney trouble" when he was ill in Liverpool Hospital twelve years ago, but has had no symptoms since then.

Present illness: Began July 16, when he was going up to the trenches, with headache, lumbar pains, sweating, weakness, dyspnea on exertion, hematuria, urgency of urination, difficulty in starting stream, pain during micturition and slight frequency.

Physical examination on admission: No hyperpnea or edema. Skin and mucous membranes clear. Heart: not enlarged; no murmurs or accentuations. Pulse 78, regular. Blood pressure: systolic 136; diastolic 88. Lungs and abdomen negative. No tenderness anywhere.

August 23. Cystoscopic examination: Bladder mucosa and ureteral orifices normal.

External genitalia, prostate and seminal vesicles normal.

Kidneys not tender or palpable.

Urine examinations

DATE	ALBUMIN	CASTS
August 19..................	"Copious hematuria"	Field Ambulance
August 19..................	"Hematuria"	Casualty Clearing Station
August 21..................		Many granular

Temperature: No records before admission. 100° August 21, returning to normal by August 26.

Case XXIX

Age twenty-eight years. Infantryman. Total service seventeen months. Field service seven months.

Admitted: September 1, 1917.

Diagnosis on admission: Albuminuria.

Past history: Scarlet fever at 12. Mechanic in civil life. Slight dyspnea on exertion for ten years, but has been able to "carry on." Slight cough two or three days before present illness.

Present illness: Began August 25, 1917, with headache, pains in the legs and back, dizziness and temperature. At the same time, he noticed pain during micturition and began to pass blood in his urine. Temperature and hematuria continued until the 29th.

Physical examination on admission: Looks acutely ill. No hyperpnea or edema. Herpes labialis but no other skin lesions. Heart: not enlarged; no murmurs or accentuations. Pulse 90, regular. Blood pressure: systolic 128; diastolic 56. Lungs and abdomen negative. Some tenderness along shins and in right lumbar region.

September 3. Cystoscopic examination: Bladder mucosa and ureteral orifices normal.

External genitalia normal. Prostate: right lobe somewhat enlarged and indurated. Seminal vesicles normal. Kidneys neither tender nor palpable.

Culture of urine: Staphylococcus albus on both glucose-ascitic-agar and glucose-agar.

October 10. Urine still positive and patient looks debilitated, although pains have been absent for more than a month.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 25.......	"Slight trace"	"Blood +"		Field Ambulance
August 26.......		"Trace of blood"		Casualty Clearing Station
August 29.......		"No blood"		Casualty Clearing Station
September 1....	0	++	0	0
September 5....	0	0	0	0
September 8....	+	0	+	Granular
October 15......	++	+	+	0

Temperature: 102.6°, August 25; 100.2°, August 26. No other records until admission. 101.6° September 1. After this not above 99° while in the hospital.

Case XXX

Age twenty-nine years. Artilleryman. Total service one year and three months. Field service eight months.

Admitted: September 1, 1917.

Diagnosis on admission: Acute nephritis.

Past history: Was rejected in 1914 as "medically unfit," but does not know why. Was a goods porter in civil life and has been a bombardier in the line. Has always been able to "carry on."

Present illness: Began August 25, with severe general pains, especially in the back and legs, frontal headache, extreme weakness and marked hematuria, without any dysuria, frequency or edema. On the night of the 26th had a chill. Dyspnea on exertion at onset.

Physical examination on admission: No hyperpnea or edema. Skin and mucous membranes clear. Heart: not enlarged; no murmurs or accentuations. Pulse 66, regular. Blood pressure: systolic 130; diastolic 78. Lungs negative. Tenderness in upper abdomen and both lumbar regions. Liver, spleen and kidneys not felt.

September 3. Cystoscopic examination: Bladder mucosa and ureteral orifices normal.

External genitalia normal. Right side of prostate and right seminal vesicle somewhat indurated. Kidneys not tender or palpable. Urine cultures; some colonies of Staphylococcus albus on both glucose-ascitic-agar and glucose-agar.

September 5. Severe general pains today.

September 8. Pains gone.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
August 25......	"Very marked"	"Very marked"		Field Ambulance
August 27.......	"Slight"	"Present"		Casualty Clearing Station
September 1....	+++	++	0	Red blood and cell casts
September 5....	+	+	+	Granular
September 9....	++	+	+	Many granular and hyaline

Temperature: Records show occasional elevations to 99.2° by mouth. Records incomplete.

Case XXXI

Age twenty years. Infantryman. Total service nine months. Field service seven months.

Admitted: February 3, 1918.

Diagnosis on admission: Nephritis.

Past history: Was rejected for army once for reasons unknown to him, but was accepted only two weeks later. Has been somewhat short of breath on route marches and has occasionally had to fall out. Heavy cold with cough, just before present illness.

Present illness: Began January 24, with slight swelling of feet, face and body, headache, dizziness, frequency of urination. Cough had almost disappeared when present illness began.

Physical examination on admission: Looks acutely ill. No hyperpnea or edema. Slight ptosis of left upper eyelid with flattening of the left side of face. Skin and mucous membranes clear. Heart: no enlargement; median to the apex impulse, in 3rd and 4th interspaces, is a rough, superficial, systolic murmur, intermittent probably cardiorespiratory. Pulse regular, not rapid. Blood pressure: systolic 140; diastolic 90. Marked tenderness in back and shins.

Blood count: W. B. C. 17,000; p.m.n. 72 per cent; lymphocytes 20 per cent; large mononuclears 7 per cent; basophiles 1 per cent.

Ophthalmoscopic examination negative.

February 5. Cystoscopic examination: Bladder wall and ureteral orifices entirely normal.

February 11. Phenolsulphonphthalein, 60 per cent. Blood pressure: systolic 126; diastolic 84.

February 24. Pains and tenderness have now disappeared.

February 28. Severe headache. No pains in legs or back. Pulse rather rapid. Evacuated to England.

Urine reports

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
February 3....	"Present"	"Smoky"	+	Occasional granular
February 5....	++	0	+	Many hyaline
February 14....	+	+	+	Granular, hyaline and cellular
February 18....	+	0	0	Granular, hyaline and red blood cell casts
February 24....	+	+	0	Frequent hyaline

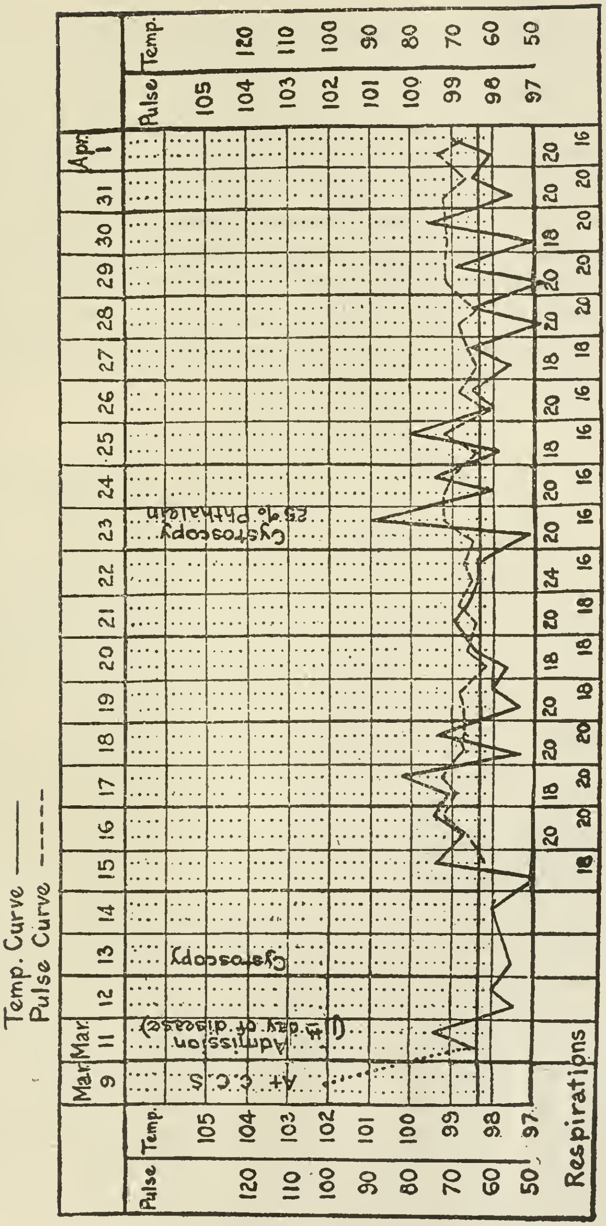
Temperature: No records before admission. 101.2°, February 3; frequent elevations to 99° or 100° until discharge.

Case XXXII

Age twenty-five years. Infantryman. Total service one year and eight months. Field service thirteen months.

Admitted: March 11, 1918.

Diagnosis on admission: Nephritis.


Temp. Curve
Pulse Curve
Admission (1st day of disease)
Cystoscopy
Cystoscopy
25% Phthalein
Respirations
Pulse
Temp.

CASE 32

Past history: No previous illnesses except occasional sore throat. Has been somewhat short of breath on exertion for some years, but has always been able to "carry on." Has also had occasional "fluttering of the heart." Was an outdoor insurance clerk in civil life.

Present illness: Began March 1, while he was on the march, with weakness and some wheezing in the chest. Two days later he noticed pains in the legs and slight swelling of the feet and the next morning puffiness of the face. The edema increased for three or four days, with some shortness of breath. At the end of that time his urine was examined and he was sent to a Casualty Clearance Station where albumin and blood were found. After entering the Casualty Clearing Station dyspnea and edema disappeared but legs continued to ache. Had some headache. On March 10 was unable to pass urine for some hours but was finally successful and noticed some initial dysuria. No urgency or frequency at any time.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
March 8	"Large amount"	"Blood present"		Report from Casualty Clearing Station
March 11	+++++	++++	0	Coarsely granular and red blood cells casts
March 12	+++++	++++	++	Red blood cell casts
March 20	+++	++++	+++	Hyaline and granular
March 23	+++	"Grossly bloody"	+++	Granular and red blood cell casts
March 26	+++	"Grossly bloody"	+++	Cellular casts

Physical examination on admission: Appears acutely ill. Slight hyperpnea, cough and hoarseness. Skin and mucous membranes pale but clear. Slight edema over the sacrum. Lungs: voice and breath sound harsh over left scapular region; râles over whole left lower lobe behind; dulness and diminished breath sounds over right lower lobe behind. Heart: apex impulse 11 cm. to the left in the 5th space; dulness extends 5 cm. to the right and 13 cm. to the left of the midline; sounds of good quality; soft, systolic murmur at the apex; no accentuations. Pulse 84, regular. Blood pressure: systolic 148; diastolic 90. Arteries soft. Abdomen negative. No tenderness anywhere.

March 12. Complains severe pains in legs.

March 13. Pains in legs less severe. Signs in chest unchanged.

Cystoscopic examination: Voided urine grossly bloody. Definitely bloody urine seen coming from both ureters. Bladder mucosa normal except for area of congestion high up on posterior wall. No hemorrhages.

March 23. Cystoscopic examination: Voided urine smoky. Urine from ureters of same character, not definitely bloody. Bladder wall and ureteral orifices normal.

Phenolsulphonphthalein 25 per cent.

March 25. Complains of urgency, frequency and terminal dysuria for the first time. As urine shows pus, this may be due to a mild infection.

Evacuated to England.

Case XXXIII

Age thirty-four years. Pioneer. Total service thirty months. Field service twenty-four months.

Urine examinations

DATE	ALBUMIN	R. B. C.	CASTS
June 12.......	"Present"	"Blood present"	
June 14.......	"Present"	"Blood present"	
June 16.......	++++	+++++	
June 17.......	+++	+++	
June 20.......	+++	+++	
June 25.......	+++	++++	Several granular and red blood cell casts

Admitted: June 15, 1918.

Diagnosis on admission: Nephritis.

Past history: Was disabled by wound of right leg in March, 1918, and has subsequently acted as cook in forward area.

Present illness: Began June 5 with dizziness, headache, shortness of breath, swelling of face and legs, dysuria, marked frequency and hematuria. Report from Casualty Clearing Station notes swelling of face and questionable edema of legs on June 10.

Physical examination on admission: Urine claret-color. Skin and mucous membranes clear. Possibly slight edema of ankles and back. No hyperpnea. Lungs clear. Heart: not enlarged; faint systolic

murmur at apex. Pulse regular, rate normal. Blood pressure: systolic, 118; diastolic, 80. Abdomen: slight tenderness in lumbar region.

June 16. Cystoscopic examination: Bloody urine seen issuing from both ureters. No hemorrhages found in bladder wall.

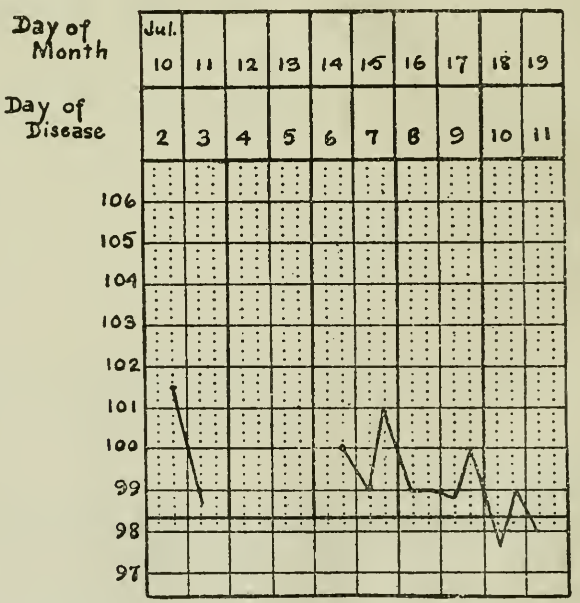
June 25. Has been up and about ward without symptoms for some days.

Evacuated to England.

Temperature: No notes before June 10. 100.8°, June 13; 100.4°, June 15; 99.8°, June 16. Otherwise not over 99°.

Case XXXIV

Age thirty-four years. Headquarters staff sergeant in front area. Total service three and a half years. Field service twenty months.



Case 34

Admitted: July 20, 1918.

Diagnosis on admission: Nephritis.

Past history: Electrical engineer in civil life. Rheumatic fever without complications in 1909. At age of twelve was struck on forehead

and says he has never been entirely well since. Had two "fits" at the age of eighteen, but none before or since.

Present illness: Began July 9 with feverish sensations, general malaise, anorexia, prostration and general pains. Next morning temperature 103.4° and noticed hematuria, but no dysuria or frequency. Vomited after entering Casualty Clearing Station, July 12. Note from Casualty Clearing Station, July 15: no edema; tenderness in shins. July 17, abdomen tender, especially over left kidney.

Physical examination on admission: Poorly developed. Appears chronically ill. No pallor. Large scar in forehead beneath which skull seems depressed. Skin and visible mucous membranes clear. No edema or hyperpnea. Lungs clear. Heart: not enlarged; no murmurs or accentuations. Blood pressure: systolic, 118. Abdomen: slight tenderness over both hypochondria and in both costo-vertebral angles; right kidney just palpable.

July 22. Cystoscopic examination: Bladder mucosa entirely normal.

Evacuated to England.

Urine examinations

DATE	SPECIFIC GRAVITY	ALBUMIN	R. B. C.	W. B. C.	CASTS
July 14.......		"Much albumin and blood"			
July 15.......	1020	"Present"	"Blood present"		
July 17.......			"Blood macroscopic"	+	"Large number epithelial and granular"

Case XXXV

Age nineteen years. Infantryman. Total service ten months. Field service five months.

Admitted: November 11, 1917.

Diagnosis on admission: Pyrexia of unknown origin.

Past history: Scarlet fever in August 1915; sick six weeks, but no renal complications. When very young had chronic bronchitis.

Present illness: About October 1, returned to rest camp after a turn in the line. Shortly after this noticed dizziness on slight exertion. No shortness of breath and no headache, nausea, vomiting or urinary

symptoms. Dizziness continued after return to line, bothering him especially on the firing step. On October 13 fainted and was taken to Casualty Clearing Station. Up to this time had not reported sick. Remained in Casualty Clearing Station until evacuated to this hospital. At time of admission to Casualty Clearing Station had a temperature of 102°. Did not feel dizzy in bed. At the end of a week, temperature had returned to normal and he was allowed up. After two days began to have frontal headache, but remained up five days more. Says that at this time specimen of urine was found negative. Headache continued after he had gone to bed, and he had some temperature and pains in the back and legs. These pains he had not had before. After fourteen days of normal temperature it rose to 102° on November 2. Was found to have moist râles in both sides of chest.

Physical examination at time of admission: This examination, together with history, gave the impression that he had trench fever. Appeared quite ill. Heart: not enlarged; systolic murmur at apex and over pulmonary area, soft and blowing in character. Lungs clear. Spleen not palpable. No areas of tenderness in legs, back or head.

November 14. Some pain in left side of face, localized to upper jaw. No tenderness of teeth. No swelling of gums. Some swelling beneath left eye.

November 15. Vomited once. Pains in legs and headache. Swelling of face slight. Urine shows albumin and casts.

November 17. Vomited once. At 7:30 p.m. had a short convulsion, followed at brief intervals by two more. Pulse 120, very weak. Blood pressure: systolic 160; diastolic 100. Phlebotomy 500 cc.

November 18. Blood pressure: systolic 140; diastolic 80. In semi-stupor. Easily aroused. Tongue moist. Pulse and heart action much stronger. Frequent extra systoles.

November 20. Slight puffiness under eyes. No other edema. Pulse and heart action slow, with occasional extra systoles. Blood pressure: systolic 150; diastolic 100.

November 21. Phenolsulphonphthalein, 45 per cent. Blood pressure: systolic 160; diastolic 110.

November 23. Semi-comatose. Neck stiff. Moderate Kernig's sign. Knee jerks moderately active. Slight external strabismus of right eye. Blood pressure: systolic 190; diastolic 130. At noon, 12 cc. spinal fluid removed under increased pressure. Severe headache. Spinal fluid shows no increased cell count. After lumbar puncture wakened slightly, and complained of terrible headache. Later relapsed

into coma. Blood pressure was unchanged immediately after lumbar puncture.

November 24. Still in deep coma. Pulse 88, full and regular. Blood pressure: systolic 145; diastolic 120. Phlebotomy 400 cc. in afternoon. After phlebotomy, blood pressure: systolic 130; diastolic 100.

November 25. Fed with gavage tube. In evening awoke from coma and refused gavage.

November 26. Very hard to arouse. Tongue moist. Blood pressure: systolic 135; diastolic 105.

November 27. Less comatose. Face a trifle more edematous. Blood pressure: systolic 150; diastolic 110.

November 30. Blood pressure: systolic 130; diastolic 100. In stupor. Complains of some headache. Vomited once.

December 1. Sleepy but can be roused. External strabismus of right eye continues. Slight paralysis of lower face. Slight drooping of upper lid of left eye. Marked exaggeration of knee jerks. No clonus.

December 5. Phenolsulphonphthalein, 45 per cent. Blood pressure: systolic 128; diastolic 95.

December 7. Has developed some boils on his back one of them being very large, due to poultices. Phenolsulphonphthalein, 45 per cent.

December 15. Examination by Captain Casamajor (neurologist to the hospital): Eyegrounds normal. Internal strabismus of left eye. Screen and parallax test shows marked exophoria about equal in both eyes. Slight left facial paralysis. Strength of arms and legs equal on both sides. Arm reflexes: left stronger than right. Knee jerks and ankle jerks: right stronger than left. No clonus. Double Babinski.

Conclusion: Lesion in cortical vessels, probably multiple cortical hemorrhages.

December 18. Cystoscopic examination: There are two hemorrhages high up on the posterior wall in the median line, very red. One large hemorrhage high up on the lateral wall, near the apex of the bladder. The remainder of the mucosa is normal.

External genitalia, prostate and seminal vesicles normal.

Kidneys not palpable; no tenderness.

Urine appears smoky.

December 19. Vomited this morning. Looks somewhat drowsy. Blood pressure: systolic 140; diastolic 102.

December 24. Had sharp pain in the left loin last night. Slight tenderness in left costo-vertebral angle; kidneys not palpable.

January 8, 1918. Cystoscopic examination: Entirely negative.

January 11. Blood pressure: systolic 150; diastolic 98. Is walking about ward. Feels well. Has occasional headaches. Appetite good. Face much fuller and looks a trifle puffy. No evidence of paralysis at present.

January 13. Blood pressure: systolic 140; diastolic 100.

February 4. Since last note has been gaining steadily in strength and has felt perfectly well. The urine has however never become negative. Today complains of pains in back. Marked tenderness in both costo-vertebral angles and in both hypochondria. No masses felt. Face seems a trifle puffy and tense. Slight coryza and cough. Heart: apex impulse 7 cm. to the left in the 5th space; dulness extends from a point 5 cm. to the right in the 4th space to a point 13 cm. to the left in the 5th space; soft, systolic murmur at the apex, not transmitted; no accentuations. Pulse 84, regular. Blood pressure: systolic 128; diastolic 100. Some sonorous and sibilant râles over left chest.

February 5. Pains better. Still complains some disability in left hand. No detectable difference in strength in two hands but an apparent delay in voluntary response in the left hand. Reflexes more active in left arm than in right.

February 16. Phenolsulphonphthalein, 47 per cent.

February 23. Blood count; Hemoglobin 80 per cent; R.B.C. 5,200,000; W.B.C. 8200; p. m. n. 66 per cent; leucocytes 34 per cent.

Slight coryza. Herpes of upper lip.

March 3. Phenolsulphonphthalein, 70 per cent.

March 4. Patient looks run down, thin and pale. Still complains of slight pain on urination; no other pains. Skin and mucous membranes clear except for herpes. Lungs: slight relative dulness in right infraclavicular region. Heart: apex 8 cm. to the left in the 5th space; area of cardiac dulness extends 5 cm. to the right in the 4th space, 11 cm. to the left in the 5th space; sounds of good quality; slight cardio-respiratory murmur at the apex. Pulse 90, regular. Blood pressure: systolic 150; diastolic 104. Liver palpable as a hard, rounded edge, 2 cm. below the costal margin, on deep inspiration. Reflexes all very active. No signs of paralysis. Discharged to England.

April 18. Report from patient in England states: No improvement in general condition. Has scarcely been free from pains in the back and has frequent headaches, associated with dizziness. For the last two or three weeks pains in the chest, especially in the region of the heart, sometimes shooting downward, sometimes to the left shoulder

and back and down the left arm to the elbow. Occasionally slight shortness of breath.

Pulse irritable, running up to 110 on very slight exertion and becoming irregular.

Four urine tests all revealed albumin.

Urine examinations

DATE	ALBUMIN	R. B. C.	W. B. C.	CASTS
October 24......	0			Verbal report of patient only
November 16...	++	+	0	Many hyaline and granular
November 25...	0	0	0	0
December 1....	++	+	0	Few hyaline
December 5....	++	0	0	Few granular
December 9....	++	+	+	Hyaline and granular
December 14....		"Guaiac strongly positive"		
December 15....	++++	"Grossly bloody"	+	Few granular
December 18....		"Smoky"		
January 15......	0	0	0	0
January 24......	+++	+	+	Few granular
February 5....	++	0	0	0
February 16....	++	++	+	Occasional granular and hyaline
February 25....	+	+	0	Hyaline and granular
March 4........	+	+	0	Hyaline and granular
April 18........	Albumin present on four examinations since March 4 (patient's report from England)			

Temperature: Records before admission to Hospital very incomplete, but temperature 102° October 15 and November 2. After this no temperature above 99.4° recorded. Unfortunately no temperature record during period of acute cerebral symptoms.

Case XXXVI

Age thirty-six years. Infantryman. Total service eight months. Field service four months.

Admitted: November 1, 1917.

Diagnosis on admission: Nephritis.

Past history: Says he was poisoned by beer two years ago and was in bed a month with swelling of the face and limbs.

Present illess: Onset October 12, when he noticed that his urine was bloody. No dysuria. On the 15th began to have headache and vomiting. No edema or dyspnea. Has vomited constantly since the 15th, but hematuria cleared up some time ago.

Note from Casualty Clearing Station: Admitted October 15. Urine shows considerable albumin. October 22, less albumin. Vomiting frequently. Almost impossible to get him to retain food or medication.

Physical examination on admission: Looks acutely ill. Very stuporous. Impossible to obtain a good history. Vomiting constantly; face slightly swollen; no other edema. Old discharging, superficial lesions resembling impetigo, on both legs. Breath urinous; mouth foul; tongue dry and thickly coated. No hyperpnea. Heart: apex and left border of cardiac dulness just to the left of the nipple line in the 5th space; no enlargement to the right; no murmurs or accentuations. Pulse 54, regular. Blood pressure: systolic 178; diastolic 110. Arteries very hard. Abdomen and lungs negative.

November 4. In semi-stupor. Tongue very dry and coated. Breath foul. Vomiting food and fluids continuously. Blood pressure: systolic 150; diastolic 100.

November 6. Breathing irregular. Condition otherwise unchanged. Vomiting continues. Blood pressure: systolic 145; diastolic 100.

November 7. Slight improvement in the morning. Seemed less stuporous. High hot colon irrigation returned with a considerable amount of clotted blood. In the afternoon vomited moderate amount of blood. Mouth and gums have been bleeding for some time.

November 8. No bleeding this morning. Has stopped vomiting. Breathing of an irregular Cheyne-Stokes type. Pulse slow and irregular in force and rhythm. Heart: rough thrill, systolic in time, over precordium; rough, harsh, superficial murmur over mid-sternum transmitted toward apex (probably pericardial). Blood count; W.B.C. 17,000; p. m. n. 86 per cent.

November 9. Has not vomited, but has been passing large, tarry stools. Marked tenderness in upper abdomen. No urine passed since last night, and attempt at catheterization failed because of stricture of urethra. Pulse more rapid. Heart: apex in the 5th space, 2 cm. to the left of the nipple line; loud, superficial, friction rub, heard over sternum. Abdomen very tender. Large, discharging ulcer on leg. Bleeding from bowel continues. Blood pressure: systolic 190; diastolic 100. Lungs show signs of pneumonia at left base.

November 10. Urine shows considerable albumin, very many red blood cells and occasional hyaline and granular casts. Died at 4 p.m. with pulmonary edema.

Temperature: No records before admission to hospital. While in hospital never above 99°.

Autopsy report (by Capt. Pappenheimer): The body is moderately emaciated and pale. Eyes prominent. Lips and gums covered with dried blood. Teeth careous. Gums spongy. There is a group of bright red, fresh petechial hemorrhages over the interscapular region and on the dorsum of the right arm. Punched out ulcer over upper third of right shin, over which skin is undermined for some centimeters. Below head of right fibula, circular scar covered by scab. Smaller similar lesion over lower part of tibia. No edema. Inguinal glands right side enlarged to size of large almond. In pericardial sac 20 cc. of turbid, slightly brownish fluid.

Lungs: Left, heavy, entire lower part dark red, with glistening pleura, lower lobe nodular. In posterior portion of upper lobe dark red, elevated areas, firmer than rest of lobe, which is dry, pale and slightly emphysematous. Lower lobe irregularly sprinkled with elevated, granular, reddish-grey patches, less than 1 cm. in diameter, between which lung tissue is in part aerated, in part dark red and airless. Bronchi pale and contain little blood-stained mucus.

Right: lighter than left, emphysematous and inelastic. Dark in posterior portion. Middle of posterior border of upper lobe shows projection about 2 cm. in diameter, distinctly firm and greyish-red, somewhat the appearance of an infarct. Lower lobe well aerated in general, rather sparsely sprinkled with small red areas of hemorrhage or very early consolidation.

Heart: not enlarged. Over both ventricles, particularly along course of vessels, are scattered bright red, blotchy hemorrhages. At base of left auricular appendix, more extensive hemorrhage where epicardium is slightly roughened. On section left auricle shows hemorrhage described, extending through auricular muscle and visible as a bluish blotch beneath thickened endocardium. Valves all normal. Ascending aorta in region of coronary sinuses and above them shows elevated, yellowish-white plaques, between which the intima is the site of shallow linear wrinkles.

Liver and spleen: Normal in appearance.

Kidneys: Left: Distinctly enlarged, measuring 14 by 8 by 5 cm. Capsule splits on stripping, leaving delicate, slightly adherent inner

layer. Surface smooth, dark brownish-red, stippled with dark red, irregular blotches, 1 or 2 mm. in size. On section color dark, pyramids darker than cortex. Markings obscured by irregular reddish streaks but not distorted. Kidney tissue moist and bloody. Glomeruli small and inconspicuous. Mucosa of pelvis shows a few, bright red, blotchy hemorrhages. Vessels not thickened or prominent. Right: Kidney similar to left, except for absence of pelvic hemorrhages.

Bladder: The mucosa shows profuse, large, bright red hemorrhages, quite irregular and in places confluent, distributed abundantly over posterior wall, beginning just above the trigone; do not follow crests of rugae. Mucosa itself is smooth, nowhere ulcerated or covered with fibrinous exudate. Mucosa everywhere strikingly edematous.

Rectum: Mucosa blood stained.

Organs of neck and pharynx, brain, adrenals, pancreas, thyroids and mesenteric lymph nodes show nothing of importance.

Stomach: Slaty discoloration of mucosa. Some fresh, small hemorrhages.

Intestinal tract: Also some scattered areas of hemorrhage into mucosa; no ulcers or other inflammatory changes.

Microscopic notes: Lung: Alveoli filled with exudate, fibrin, red blood cells, polynuclears and desquamated alveolar cells. In some areas red cells predominate, giving frankly hemorrhagic character to pneumonia. In areas of most extensive hemorrhage, alveolar walls disrupted. Consolidation patchy, but quite extensive.

Liver: Marked edema of liver cells, tissue between them and capillary walls.

Spleen: Shows nothing of importance, except considerable intracellular brown pigment.

Kidney: Most of glomeruli show free blood in capsular space. Tufts are collapsed, and contain very few red blood cells. Entire absence of any acute inflammatory change in glomeruli. Number of leucocytes not increased, nor is there any exudate apart from hemorrhage into the capsular space. Lining of Bowman's capsule for the most part normal. In a few of the tufts, epithelial cells seem to have grown over the mass of conglomerate red blood corpuscles. Outlines of tuft capillaries are rendered somewhat indistinct by hyaline swelling of capillary walls. Proximal convoluted tubules are lined with high columnar epithelium, excellently preserved, differing from normal not only in shape, but in the presence of large numbers of hypertrophic nuclei, lobate and frequently having the appearance of amitotic division. Distinct mitotic

figures not found. Tubules, almost without exception are filled with well preserved red blood corpuscles, and variable numbers of desquamated epithelial cells and occasionally a leucocyte or small lymphoid cell. Remainder of tubular system shows excellent preservation of epithelium in collecting tubules: Red cells found in the tubules are loose, well preserved, forming pink-staining, granular masses, in which individual corpuscles are not easily recognized. Few of tubules also contain casts mixed with blood pigment. Interstitial tissue is definitely increased in amount. Tubules rarely in apposition, but separated from one another by rather edematous fibrous tissue, which contains lymphoid and plasma cells, for the most part sparsely distributed, but in a few places forming a rather dense accumulation. There are also scattered pigment-containing cells. There is, however, very little, if any, hemorrhage into the interstitial tissue. The arteries show no sclerotic change or any other distinct lesion.

Bladder: Section through the bladder wall shows an intact mucosa. There is a loose edema of the submucous tissue, with a sparse infiltration of mononuclear cells.

Section of bladder wall (through hemorrhage) taken from specimen preserved in Jores: the epithelium is missing over the entire section (artifact). The submucous cellular tissue is extremely edematous. There is an extensive hemorrhage into the superficial portion of loose cellular tissue. Although there are occasional lymphocytes among the red blood cells, the lesion does not appear to be an inflammatory one. Two small lymph follicles are included in the section. The muscular coat shows no change.

Heart: Section through wall of auricle in region of hemorrhage shows an acute necrotic and suppurative process with no effort at repair. Extreme fragmentation of nuclei of leucocytes. These nuclear fragments and red blood cells extend in strands between muscle bundles on the surface. Lifting up the still intact row of epicardial cells is an exudate rich in fibrin. Muscle fibers show more degeneration, having lost their striations; many of them are necrotic. Section through the ventricle shows marked fragmentation of muscle, but no inflammatory changes.

Aorta: Section through plaque in first portion of aorta shows typical syphilitic aortitis.

RIEDEL'S LOBE OF THE LIVER COMPLICATING UROLOGICAL DIAGNOSIS

VINCENT J. O'CONOR

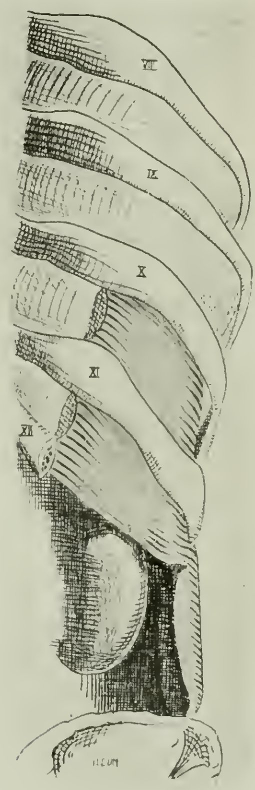
From the Urological Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

"Riedel's lobe," or linguiform lobulation, is a tongue like elongation of the anterior margin of the right lobe of the liver. It is not a distinct lobe in the true sense of the word, but merely a prolongation of the right lobe itself.

Riedel (1) after whom the lobulation is named, originally described the condition in eight cases, all of which were associated with enlargement of the gall bladder. He ascribed this prolongation to the gradual enlargement of the gall bladder tending to cause downward traction on the anterior margin of the right lobe.

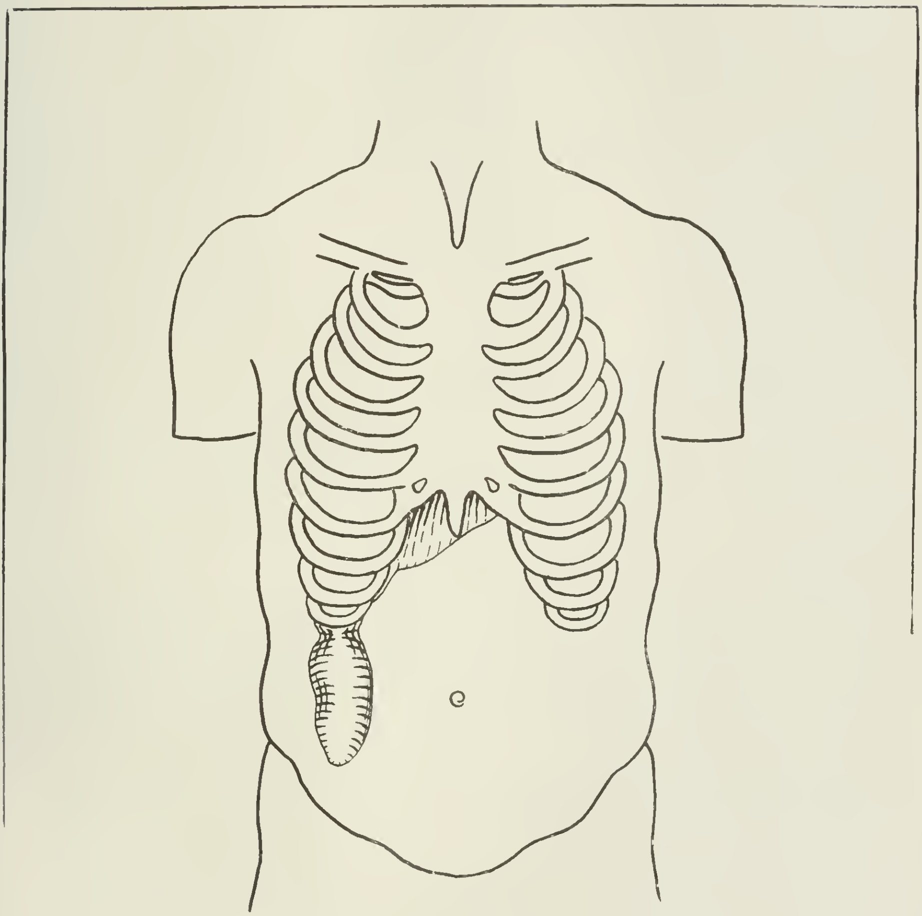
In accordance with this view several surgeons have noted linguiform lobulation in connection with gall bladder disease, and the same association has been occasionally reported at necropsy. Leaf (2) however, has demonstrated four specimens at autopsy in none of which was there evidence of disease in the gall bladder or surrounding structures, and Thompson (3), reports a similar case. As all of the subjects were women, both of these writers agreed that the etiological factor was probably compression due to the wearing of corsets. This linguiform lobulation has occasionally been found in quite young children (4) and must, therefore, be regarded as an anatomical abnormality in some, if not all, of the cases. In every instance mentioned the prolongation was freely movable and the structure of the lobule was of normal hepatic tissue. There are several cases on record where a gumma, abscess, or tumor was found in a linguiform lobule. From the descriptions, however, these prolongations were slight and not typical of the lobulation known as "Riedel's lobe."

The condition frequently described at autopsy as occurring in women who had practised tight lacing, and in foreign soldiers who were habitually tightly jacketed, must not be confused with linguiform lobulation. This condition of so-called "corset-



DIAGRAMMATIC DRAWING SHOWING ANTERIOR VIEW OF LINGUIFORM LOBULATION OF THE RIGHT LOBE OF THE LIVER FOUND IN THE CASES HERE REPORTED

liver" presents a broad downward projection of the right liver lobe separated from the main portion of this lobe by a transverse band of fibrous tissue. When extremely marked this may give rise to the same confusing clinical picture as Riedel's lobe. Clinically, it is very rarely found in this country.



Posterior View Showing Linguiform Lobulation of Right Lobe of the Liver Anterior to Normal Kidney. The Notch Above the Elongation Being Anterior and Only Slightly Lower than the Upper Pole of the Right Kidney

A careful review of the development of the liver and its lobules in man reveals no morphological reason for the occurrence of a linguiform lobulation (5). From the evidence at hand, it would seem that it may occur as an anatomical abnormality, or that it may be acquired through conditions which tend to force the anterior margin of the right lobe downward.

Text books on diagnosis, which mention Riedel's lobe, after stating that the condition does occur, dismiss the subject by telling us that it is easily ruled out by careful physical examination. Unfortunately, the differentiation is not so easily accomplished. Moynihan (6) says that a Riedel's lobe is frequently mistaken for kidney or tumor. R. C. Cabot (7), reports a case diagnosed as carcinoma of the cecum. Undoubtedly others have had similar experiences.

This brief summary of the data concerning Riedel's lobe is given merely to recall the condition to mind, and to preface the report of two cases which are of interest to the urologist.

Case I

Caroline B., aged thirty-eight years, entered the hospital complaining of severe pain in the right side which had been present without relief for four days. The pain was constantly dull, but frequently was sharp and of a "doubling up" character. At these times it radiated into the right groin and the inner surface of the right thigh. There had never been any pain previous to this attack. Frequency of urination had developed at the onset of the pain (eight to ten times during the day, and four to six times at night). There had been no burning or pain on urination and no hematuria. The odor of her urine had become very offensive to the patient. The admission temperature was 101.8°; pulse 120; respiration 28. Blood examination showed hemoglobin 75 per cent, leucocytes 9,000. The catheterized bladder specimen showed many leucocytes, no erythrocytes and no casts or crystals. The patient was acutely ill and was suffering from pain in the right flank.

The family history was of no importance. She had had one miscarriage twenty-three years ago and an appendectomy, right salpingo-oöphorectomy and repair of right inguinal hernia had been done twenty-two years ago. An extra-uterine pregnancy was removed

abdominally fourteen years ago. Otherwise, she had always enjoyed good health except for severe pruritis vulvae for one year previous to admission. She had had no abdominal pain since operation twenty-two years ago and no previous urinary trouble.

Physical examination showed a rather undernourished woman in very evident distress, especially on exertion. The physical findings were normal except for diffuse tenderness over the right upper abdomen and severe pain on pressure in the right costo-vertebral angle. A mass was palpable on the right, midway between the costal margin and the crest of the ilium. It could be readily outlined and because of the thin abdominal wall, could be grasped and partially encircled by the palpating fingers. The mass was not tender on pressure and moved very slightly with respiration. The upper pole of the mass could be definitely outlined and depressed on palpation. The liver above was apparently not enlarged and the right border was just palpable beneath the costal margin. There were no other palpable masses in the abdomen.

In the X-ray the shadows of both kidneys were seen, large and low, but no shadows that could be interpreted as stone.

Cystoscopy revealed that the bladder mucosa showed signs of mild infection (a slight diffuse reddening but no discrete areas of hyperemia or exudation). Both ureteral orifices were normal but cloudy urine was seen to come from both; that from the right was very turbid. Catheterization of the ureters showed both urines to be cloudy, the specimen from the right side showing much more pus than that from the left. The catheters were passed 28 cm. without difficulty.

Function. The left showed an appearance-time of the dye (phenolsulphonphthalein subcut.) in eight minutes, and 6 per cent excretion in thirty minutes. The right, an appearance-time of fifteen minutes, 3 per cent excretion in thirty minutes.

Because of the severe pain the patient was undergoing and because of a rapid rise in temperature to 104.4° shortly after admission, pyelograms were not attempted.

Vaginal examination showed the uterus in good position and there was no evidence of any abnormality in the surrounding pelvis.

The preoperative diagnosis was right pyonephrosis with possibility of a perinephritic abscess

Operation. A right lumbar incision was made. The right kidney was readily mobilized and although slightly enlarged was normal in every respect. The mass palpated previous to operation could be felt

just anterior and below the kidney in the peritoneal cavity. The peritoneum was incised posteriorly and the mass proved to be an elongation of the right lobe of the liver, reaching almost to the ramus of the pubis. The prolongation was freely movable and appeared to be of normal hepatic tissue. The gall bladder and surrounding structures were normal. The right ureter was only very slightly dilated, and no calculus was present.

Patient made an uneventful convalescence and was discharged three weeks after operation. At this time the bladder urine contained relatively few pus cells.

Final diagnosis. Riedel's lobe of the liver—Bilateral pyelitis (acute).

Case II

Maggie M., aged fifty-two years, entered the hospital complaining of pain in the left loin and abdomen which had been present for two years. The pain came on shortly after an operation for hemorrhoids. It was of an indefinite type, never sharp or excruciating and was relieved by pressure over the area of pain. She stated that she thought there was a definite relation between the pain and periods of constipation, but was not entirely clear on the subject. Frequency of urination developed at the time of the onset of the pain (six to ten times during the day and four to six times at night). There was never any dysuria, hematuria or pyuria. She had lost 16 pounds in weight since the onset of the pain.

The admission temperature was 98°; pulse 85; respiration 20. Examination of the blood showed hemoglobin 75 per cent, leucocytes 9,500. Catheterized specimen of bladder urine was found to be normal. Stool on repeated examination was normal.

The family history was that the mother had died at forty-four of diabetes, and the father at sixty-seven of "liver trouble." One sister died of carcinoma of the uterus. She had been married for thirty years, the husband was living and well. She had had 12 children, 11 of whom were living and well, one had died of "rickets." She had always been more or less constipated. Her skin had become yellow three to four years before admission and had remained so. Her menopause was one year past. There were no gastric, pulmonary, cardiac or neuro-muscular complaints.

Her occupation was general housework.

The patient was a well developed but poorly nourished woman with a diffusely muddy, yellowish colored skin. There was a flaky scaling over her chest and back, and here the skin was loose and flabby. The sclerae were clear. Her teeth were in poor condition and showed considerable pyorrhea, but the buccal mucus membrane was normal. The heart was not enlarged, but there was a loud systolic murmur at the apex and an accentuated pulmonic second sound. The blood pressure was systolic 110—diastolic 80. In the right loin there was a large easily palpated mass, freely movable, and slightly tender on bimanual pressure. The surface was smooth and slightly tender on pressure, the upper pole could be distinctly outlined and partially grasped by the palpating fingers. There was no tenderness in the right or left costo-vertebral angle. The left kidney was palpable and not enlarged or tender. The liver margin was felt two finger breadths below the costal margin but was smooth and did not appear to be connected in any way with the mass felt lower down. There was no distension, visible peristalsis, or evidence of free fluid in the abdomen.

The X-ray examination of the gastro-intestinal tract showed a narrow descending and a rather large ptotic transverse ascending colon and cecum, but no evidence of any obstruction. There was nothing abnormal in the X-rays of the urinary tract.

Cystoscopy showed the bladder mucosa to be normal with normal musculature, and the ureteral orifices appearing as small slits. The trigone was not injected, and no efflux was seen on watching the right orifice. Clear urine was seen to come from the left ureter. An ureteral catheter was passed 30 cm. on the left without difficulty; on the right, a No. 6 catheter could only be introduced 22 cm. There was no flow of urine obtained from the right side although the catheter was proved patent. On the left side there was an abundant flow of clear urine. The phenolsulphonphthalein appeared on the left in five minutes and showed 20 per cent excretion in fifteen minutes.

No solution could be introduced into the right ureter. The left uretero-pyelogram was normal.

Vaginal and rectal examinations were negative.

Preoperative diagnosis.—There was considerable variance regarding the diagnosis, genito-urinary findings coupled with the large mass, evidently kidney, suggested a neoplasm of the right kidney, probably hypernephroma. Others of the staff felt that the symptoms were those of a subacute obstruction most probably associated with neoplasm. Other than a generalized pigmentation and low blood presssure, there

was no basis for a diagnosis of Addison's Disease which had been considered.

Operation.—Under gas oxygen anesthesia a right rectus incision was made. There was no free fluid or other suggestion of peritoneal irritation. The liver was an unusually low one with an "extra" lobe on the right which extended down to the anterior superior spine, and was the mass that had been felt and considered as a possible neoplasm of the right kidney. Both kidneys were in good position and entirely normal. The gall bladder was soft and compressible and there was no sign of any inflammatory process in this region. The duodenum, pancreas, stomach, and pelvic organs were normal. No evidence of obstruction could be found in the intestinal tract. The cecum and ascending colon were unusually large and mobile and there was a marked visceroptosis present. The appendix was an atrophic one and was removed incidentally.

The patient made an uncomplicated operative recovery and was discharged on the twenty-fifth day after operation with instructions concerning diet and means to alleviate constipation.

Final diagnosis.—Riedel's lobe of the liver—splanchnoptosis.

CONCLUSIONS

Riedel's lobe offers a positive complication to the urologist in making a diagnosis even in carefully studied cases. The occurrence of this condition is sufficiently frequent to be borne in mind when determining the nature of a palpable mass in the right flank or abdomen. In the presence of acute infection in the urinary tract, the occurrence of a linguiform lobulation makes a differentiation very difficult and the apparent indications are for an immediate surgical procedure. The mass in each of these cases could be definitely outlined on palpation and moved slightly on respiration. The notch in the elongation gave the physical signs usually found on palpating the upper pole of a low lying or enlarged kidney. In the cases described, circumstances prevented our getting uretero-pyelograms on the right. These would have served to assist us in ruling out the supposition that the palpable mass was kidney.

In both of these patients the gall bladder and surrounding structures were normal, contrary to Riedel's original conception

of the etiology of the prolongation. In both individuals the structure of the elongation felt and appeared to be normal liver tissue.

REFERENCES

(1) Riedel, H.: Berliner Klinisehe Wochenschrift. July, 1888, Nos. 29 and 30, p. 577.
(2) Leaf, C. H.: Proeeedings of the Anatomical Society of Great Britain and Ireland. London, 1898–1899, Journal of Anatomy and Physiology, 1898, p. xvii.
(3) Thompson, Arthur: Journal of Anatomy and Physiology, 1885, vol. xix, p. iii.
(4) French, Herbert: Index of Differential Diagnosis, p. 366.
(5) Ruge, Georg: Normale und abnormale Entwicklung des Menschen. 1911, Morphologisehes Jahrbuch, xlii, 397.
(6) Moynihan, Berkeley: Gall stones and their surgical treatment. p. 145.
(7) Cabot, R. C.: Differential diagnosis, vol. i.

PRESENTATION OF DEVICE FOR HOLDING URETERAL CATHETERS

CHARLES S. LEVY

From The Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Maryland

The method usually employed for ureteral catheterization not infrequently leads to errors in technique, which result in contamination of the catheters. The contrivance herewith described is of simple construction, does not complicate instrumentation and will assist in preserving an aseptic technique.

The apparatus (fig. 1) is a glass tube about 1 cm. in diameter and of sufficient length to contain the ureteral catheters. At its lower end it makes a short curve of about 120 degrees with the long axis of the shaft of the instrument and terminates in a pronged device with two projections. The ureteral catheters are threaded backward into the holder through these prongs and their catheterizing ends allowed to project for 4 to 5 cm. (fig. 2). The escape of fluid from the bladder may be prevented by plugging the distal ends of the catheters with tooth picks.

The holder is boiled before use. In clinics where ureteral catheters are dry sterilized, the holder with the catheters and tooth picks in place can be sterilized ready for use. If desired, the prongs of the instrument can be capped with the same rubber tips that are used on the catheterizing barrel of the cystoscope and the holder filled with antiseptic solution, such as boric acid or bichloride.

The holder and the catheters are brought to the center of the cystoscopic table by two clamps, such as one finds in a chemical laboratory, and a straight metal rod. As shown in figure 2, the lower clamp can be conveniently attached to the vertical upright of the stirrup beneath the patient's knee and the upper clamp made to carry the holder, whose lower end is placed above

the eyepiece of the cystoscope with the prongs turned toward the patient; this position gives a curve to the catheters that tends to prevent their coming in contact with the operator's face.

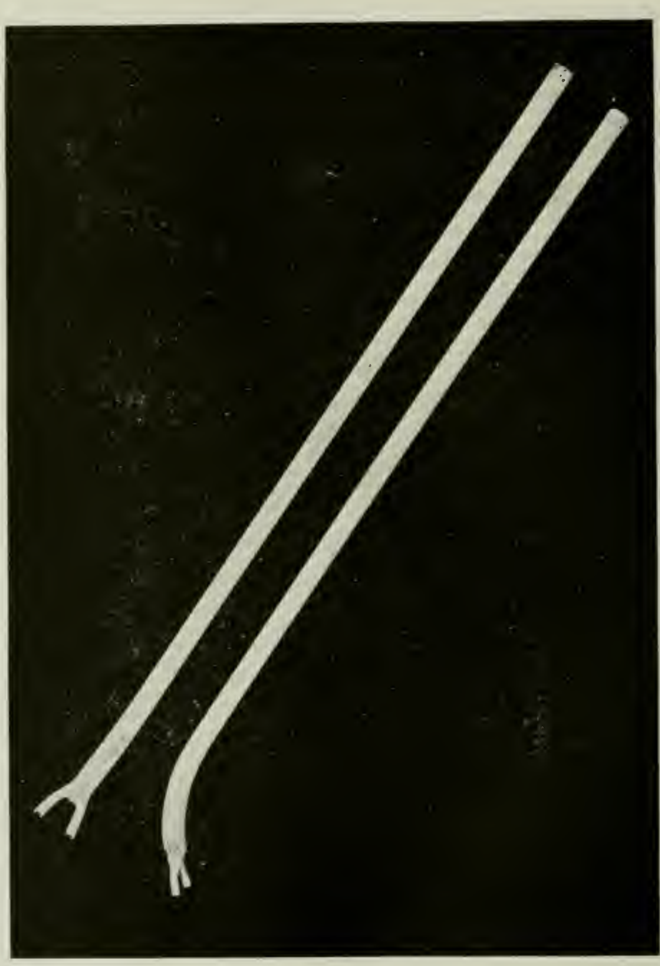


Fig. 1. Anterior and Lateral Views of Catheter Holder

After the cystoscope and catheterizing barrel have been introduced, the ureteral catheters are brought down and passed into the bladder (fig. 3). The catheters have ample slack and can

be moved up and down at will, but are yet held sufficiently taut to avoid touching the operator.

With the method described the ureters are catheterized as easily and as rapidly as with any other procedure. It has the

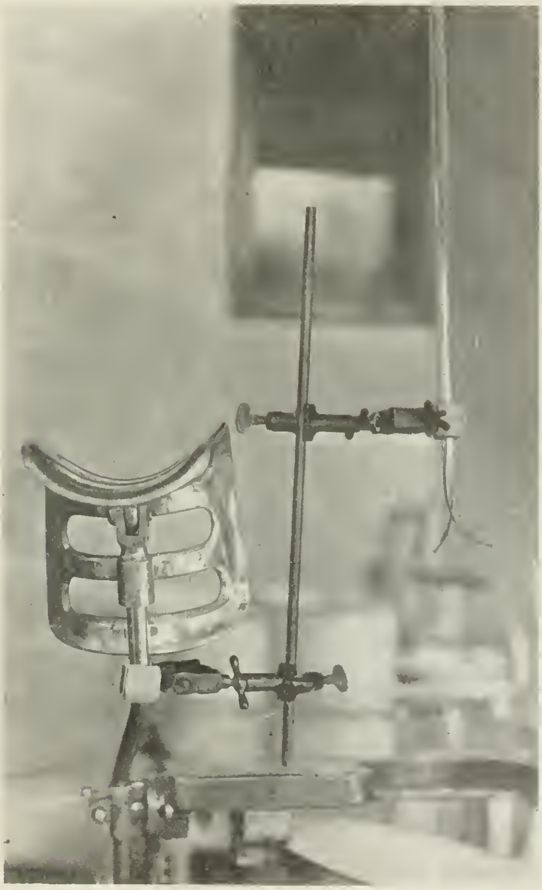


Fig. 2. Showing the Attachment to Stirrup of Table and the Clamping Device by Which the Holder and Catheters are Brought to Center of Table

advantage of enabling one to work without an assistant and of maintaining a sterile technique throughout. It should be em-

phasized that the setting up of the holder consumes no more time than the preparation for ureteral catheterization as ordinarily done.

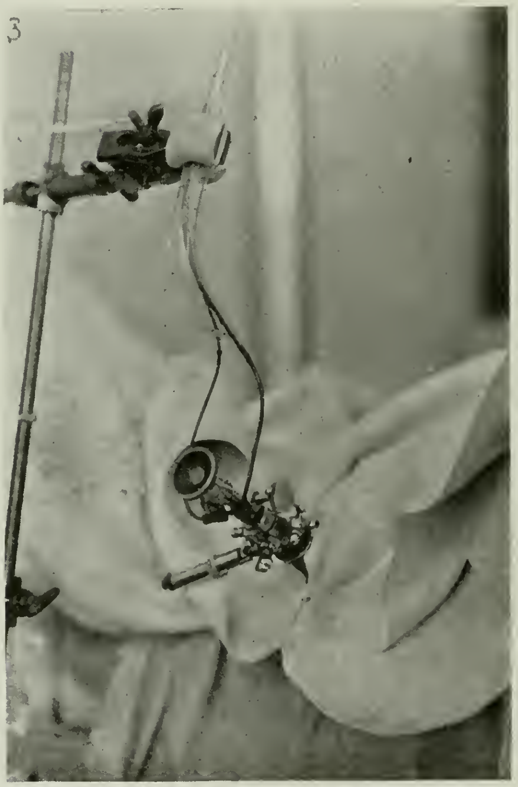


Fig. 3. Catheters Brought Down from Holder and Introduced into Cystoscope

RENAL MIGRATION OF URETERAL CALCULUS: CASE REPORT

JOHN H. NEFF

University, Virginia

Miss C. H., graduate nurse, age twenty-four, entered the University of Virginia Hospital, July, 1919, with a diagnosis of right pyelitis. She gave a history of infrequent attacks of right abdominal pain accompanied by chills, temperature, and urinary frequency since 1907. Since April, 1918, these attacks had been more severe, with a maximum temperature of 104.8° and, once, with considerable hematuria. No relief had been obtained from an appendectomy in 1915.

Catheterized bladder urine upon admission contained much pus. Cystoscopy, Brown-Buerger, showed a moderate basal cystitis. The left kidney urine gave negative findings, culturally and microscopically. On the right side an impassable obstruction was met 2 cm. above the ureteral orifice. X-ray examination of the urinary tract, August 3, 1919, revealed a stone low in the right ureter (fig. 1), no shadows in the kidney region. On second cystoscopy, Kelly, August 4, obstruction was encountered as before in the right ureter. After cocainizing the low segment, a no. 8 catheter carrying a no. 13 wax bulb was finally passed. Ten cubic centimeters of olive oil were injected above the stone. The wax bulb met much resistance on withdrawal and was deeply grooved on one side. The kidney urine gave a pure culture of staphylococcus. The patient had a sharp reaction after the treatment, temperature reaching 103°.

Patient returned, August 29, for further dilatation. X-ray on that date showed the position of the stone unchanged. The low right ureter was again cocainized, olive oil injected above the calculus, the point of obstruction stretched with the Lewis dilator and, finally, dilatation to about 17F. obtained with a bougie. The reaction following this treatment was violent—repeated chills and temperature as high as 105°. Vaginal examination two days later demonstrated pronounced tenderness and induration at the base of the right broad ligament. This finding, along with the rather unusual reaction, suggested

the possibility of some leakage at the site of dilatation. On the fourth day this area was exposed through a vaginal incision; only a non-suppurative periureteritis was found. Temperature was normal on the seventh day.

Fig. 1. Stone Low in the Right Ureter, August 3, 1919
Kidney plate this date was negative

Patient was again admitted October 15, 1919, six weeks after the above treatment. In this period she had been practically free from all symptoms and had gained 17 pounds. She had watched her urine carefully and was positive that she had not passed a stone. A picture of the lower urinary tract was made but no evidence of calculus seen. If the patient's statement were correct that the stone had not been

voided, the remaining possibility was that the stone had ascended the ureter to a point out of range of the low first exposure. A kidney plate was therefore taken, and this located the calculus evidently in the pelvis (fig. 2).

FIG. 2. STONE IN THE RIGHT PELVIS, OCTOBER 15, 1919
Low ureteral plate this date was negative

Pyelotomy was done the next day and the stone removed from one of the middle calices. The exposed portion of the ureter presented surprisingly slight dilatation. It would have been rather difficult manually to force the stone into the ureter. The stone measured 5 x 7 x 10 mm.

COMMENT

This is evidently a case of renal migration of an ureteral calculus. While the possibility of such an occurrence is well recognized, the observed instances seem rare enough to warrant recording; particularly so, since in any such case the chance for serious clinical error is inherent. The final renal position in our patient might well have been overlooked in that only a low picture was first taken on the last admission.

The conclusions of Kretschmer[1] that retrograde movement of ureteral calculi is due either to dilatation of the ureter or, lacking this, to reverse peristalsis, seem obvious and logical. In the case above briefly outlined, the migration finds ready explanation on the basis of ureteral dilatation. The violent reaction after treatment and the marked periureteritis found upon exploration through the vagina, would certainly suggest rather complete temporary occlusion of the ureter, this accompanied of course by wide dilatation above. The dislodged stone would thus have an amply large channel for ascent to the kidney and the gravity element was no doubt furnished by the patient tossing about in bed, hips elevated now and then upon pillows or the bedpan. The ureteral instrumentation could not have carried the stone higher than four inches at the most since no instrument was passed to a greater height.

[1] Kretschmer, H. L., The retrograde movement of ureteral calculi. J. A. M. A., lxxi, 1355.

PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES OF THE PROSTATE GLAND

I. EFFECT OF PROSTATE FEEDING ON THE GROWTH AND DEVELOPMENT OF TADPOLES[1]

DAVID I. MACHT

From the James Buchanan Brady Urological Institute and the Pharmacological Laboratory, Johns Hopkins University

Gudernatsch (1) was the first to call attention to the remarkable influence exerted by the feeding of thyroid and thymus glands on frog's larvae. That observer noted that feeding of thyroid glands produced a dwarfing or shrinkage in size of tadpoles on the one hand, and a very rapid differentiation or metamorphosis of tadpoles into frogs on the other hand; while feeding of thymus glands retarded metamorphosis and at the same time stimulated growth, with the resultant formation of giant tadpoles. These observations have since been confirmed and extended by Rogoff (2) and many other investigators. Gudernatsch and other observers have also studied the effect of feeding of other organs and glands on the development and growth of tadpoles, and have found that the above interesting effect of thyroid feeding was not produced by any other gland. Recently however, McCord described a similar phenomenon exhibited by tadpoles fed on pineal gland (3). So far as the present author has been able to ascertain, no experiments concerning the feeding of *prostate* gland to tadpoles or concerning the relation of the prostate to the growth of other animals are on record. In connection with a physiological and pharmacological study of the prostate gland and of prostatic extracts, the present author conducted a series of experiments in feeding various tadpoles with desiccated prostatic substance. The result of these experiments it is proposed to report in this place.

[1] This work was first reported in a preliminary communication in the Proceedings of the Society for Experimental Biology and Medicine, 1919, xvi, pp. 138–139.

Fig. 1

Fig. 4

Fig. 2

Fig. 5

Fig. 3

Fig. 6

METHOD

Tadpoles of the following amphibia were employed: *Rana sylvatica, Rana palustris, Rana catesbiana, Bufo lentiginosus* and *Amblystoma punctata.* Experiments on them were begun at different ages, some being used immediately after hatching, others when they were from one day to three weeks old. In every experiment, several tadpoles of exactly the same age and the same species were placed in two vessels. The tadpoles in one vessel were used for feeding prostate; those in the other vessel were used as controls. In all experiments the two sets of tadpoles were kept under exactly the same conditions. They were placed in vessels of the same size, containing the same amount of water, and were kept in the same room under the same conditions of temperature and sunlight exposure. Both sets of tadpoles were fed in some cases on weeds and in others on fresh pig's liver, or on both. The only difference in the treatment between the two sets was that the tadpoles in one case were fed on small amounts of desiccated prostate gland mixed with the water, while the control animals were either given no prostate at all or were fed on other desiccated glandular

Fig. 1. Rana sylvatica

Effect of prostate feeding from April 20 to May 19. Ram's prostate was used

Fig. 2. Rana sylvatica

Feeding of ram's prostate form April 25 to May 6. Note difference in development.

Fig. 3. Rana palustris

Feeding of ram's prostate. Note the metamorphosis of the prostate-fed tadpole as compared with the control. April 20 to June 11.

Fig. 4. Rana palustris

Large tadpoles were fed with ram's prostate for two weeks on the one hand, and parotid gland on the other. No difference in size and development.

Fig. 5. Rana catesbiana

Effect of feeding ram's prostate for three weeks

Fig. 6. Bufo lentiginosus

Metamorphosis produced by feeding ram's prostate from May 12 to June 6. Both tadpoles were about a week old at the beginning of experiment.

FIG. 7

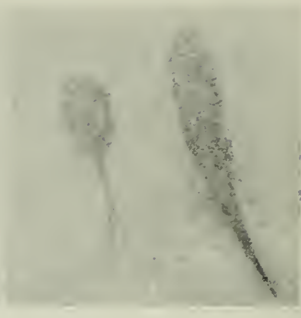


FIG. 9

FIG. 8

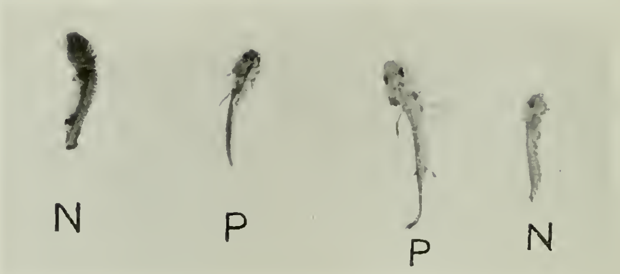


FIG. 10

substances studied as controls. Thus, for instance, in some experiments as a control to prostate feeding, tadpoles were fed on desiccated parotid substance, or ovarian substance, or corpus luteum or other glands.

For the study of the prostate gland desiccated and powdered prostata were used from the following animals: the ram (Armour's preparation), the bull, the steer, and in a few cases, the desiccated hypertrophied prostate of man obtained from the operating room.

RESULTS

The effect of prostate feeding manifested itself in changes both in growth and differentiation of the larvae. As in the case of the thyroid gland, it was found that feeding with prostate tended to hasten the differentiation or metamorphosis of the tadpoles into frogs. This effect was noticeable in some cases even after a few days. While this stimulating effect on metamorphosis was not as rapid as that following the administration of thyroid gland on the one hand, it was found, on the other hand, that feeding with prostate was not as deleterious to the

Fig. 7. Rana palustris

Tadpoles two weeks old at beginning of experiment, showing effects of feeding desiccated prostate substances of the ram, the steer and the bull for a period of time lasting from May 1 to May 20. A, normal; B, prostate of ram; C, prostate of bull; D, prostate of steer.

Fig. 8. Bufo lentiginosus

Effect of feeding prostate substances of ram, steer and bull, as compared with the normal growth of the tadpoles. A, normal; B, prostate of ram; C, prostate of bull; D, prostate of steer, Duration of experiment, May 12 to June 2.

Fig. 9. Bufo lentiginosus

Showing effect of feeding of desiccated human prostate from a case of hypertrophy. Duration of experiment, May 20 to June 6.

Fig. 10. Amblystoma punctata

Larvae about one week old were fed on desiccated prostate substance of the ram. Note difference in size and development of front and hind legs, as compared with the small control tadpole, which was originally of exactly the same size as the other. Magnification about one and a half of natural size. Duration of experiment, May 14 to May 28. N=normal; P=prostate feeding.

animals, so that prostatic substance could be administered to the larvae continuously, whereas, as is well known, feeding with thyroid must be carried on at intervals, lest the animals die. Furthermore, unlike the effect of thyroid feeding, prostate feeding did not cause a diminution or shrinkage in size of the tadpoles, but on the contrary often showed a tendency to stimulate their growth to a size above normal. These effects will be seen in the illustrations.

The effect upon the size and the metamorphosis of the larvae was noted in all the frog tadpoles mentioned above and also in the case of the common toad, *Bufo lentiginosus*, and in a few salamander larvae which were studied. The stimulation of metamorphosis was of course more strikingly evident in the case of those frog tadpoles which normally metamorphose in a short period of time, but was also demonstrable in the case of the bull-frog, *Rana catesbiana*, which ordinarily takes two years to change from a tadpole into a frog. The salamander larvae which also take many months before they begin to show signs of metamorphosis, gave definite evidence of a more rapid differentiation after feeding with prostatic substance as early as after two weeks, as shown by shrinkage and stumping of the gills and development of fore and hind legs. This is illustrated in figure 10.

DISCUSSION

A sufficient number of experiments with controls on various species of amphibians have been conducted to exclude any accidental effects in connection with the above experiments. It seems to be definitely established that feeding of prostatic substance exerts an influence on the growth and differentiation of tadpoles. This, of course, seems to speak in favor of an internal secretion of the prostate gland. The only other evidence in favor of such an internal secretion, though not as conclusive as the one obtained in the present research, is the observation of Serralach and Pares (4), who found that prostatectomy in dogs was followed by cessation of spermatogenesis and atrophy of

the testes, and that injection of glycerin extracts of the prostata prevented these phenomena.

It is interesting to note that the iodine content of the prostate gland, unlike the thyroid, is but small and indeed is much less than that of many other glands in the body. The following table from Oppenheim's Handbuch der Biochemie, and based chiefly on the work of Justus (5), shows the relative content of iodine in the various tissues. What the significance of this low iodine content of the prostate may be when compared with the high iodine content of the thyroid gland, it is at present impossible to say.

Table showing iodine content of tissues

	IODINE IN 0.01 MGM.	
	Calf	Human
In 100 grams of:		
Thyroid	105.3	976.0
Nails	100.0	80.0
Thymus	46.8	
Skin and hair	42.9	87.9–84.4
Testicle	39.8	50.0
Lymph glands	33.3	60.0
Liver	22.0	121.4
Mamma	22.0	
Spleen	15.0	56.0
Lungs	15.0	32.0
Kidneys	6.4	105.3
Bone marrow	0	
Stomach		90.9
Prostata		68.9
Ovaries		64.8
Suprarenals		63.6
Brain		20.0
Uterus		41.3
Pancreas		43.1
Intestine		11.9

It is furthermore interesting to note the difference in the effects of the prostates from the steer and the bull. As will be seen from the illustrations (figs. 7 and 8), the prostate of the steer was weaker in its action than that of the bull. This

is, of course, as might have been expected, inasmuch as the prostate of the steer undergoes more or less atrophy after castration. In a few experiments made in feeding with the human prostate from a case of mild hypertrophy of that gland, the same effects on growth and differentiation were noted as those seen after feeding the prostate of the ram (fig. 9). The author is investigating the effect of prostate feeding on rats, rabbits and other higher animals, and the results of the observations will be published in due time.

SUMMARY

1. The effect of feeding of desiccated prostatic substance from various animals on the growth and development of a number of species of tadpoles was studied.

2. It was found that prostate feeding tends to stimulate both the growth and metamorphosis of the larvae of the frog, toad and salamander.

3. These observations speak in favor of an internal secretion of the prostate gland.

REFERENCES

(1) Gudernatsch: Arch. f. Entwickmech. d. Organismen., 1912, xxxv, 457.
(2) Rogoff: Jour. Pharmacol. & Exp. Ther., 1918, x, 199.
(3) McCord: Trans. Am. Gyn. Soc., 1917.
(4) Serralach and Pares: Comptes Rendus Soc. Biol., 1907, lxiii, 790.
(5) Justus: Virch. Arch., clxx, 501, and clxxvi, 1.

REPORT OF A CASE OF CONGENITAL STENOSIS OF BOTH URETERAL ORIFICES

ISABEL M. WASON

From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine, New Haven, Connecticut

Hydronephrosis in the early years of life due to congenital malformations of the urinary tract is a well recognized condition. A change of this character in one kidney only may follow a stricture, partial or complete, of the ureter. When both organs are similarly affected, the obstruction is most frequently in the urethra, but may be present in both ureters. In the majority of cases of ureteral stricture, the lesion is placed at one of the acknowledged points of predilection above the juncture of this duct and the vesical cavity. A small but interesting group of cases, however, presents an obstruction at the point of entrance into the bladder with resultant dilatation of the end of the ureter. The case of stenotic orifices described below belongs in this group.

Congenital malformations of the urinary system are not infrequently multiple. Partial or complete reduplication of both ureters is a well known condition in urological clinics and at the post mortem table. These supernumerary ureters are often the seat of stenoses, strictures, or atresias; their vesical ends may be misplaced in the bladder, in a neighboring organ, or they may end blindly. A change in the primary or accessory ureter may be found on one side alone, in association with a similar or slightly different change on the other side, or with a malformation elsewhere in the urinary tract. It is, therefore, interesting but not surprising to find narrowing of the mouth of both ureters associated with a less important anomaly of the urethra. The presence of a valve in the membranous urethra, when it is of sufficient size to offer definite obstruction to the

urinary flow, may lead to extensive alterations in the structure of the upper urinary organs. In the case reported below, the valve is present on one side only and apparently played a much less significant rôle in the dilatation of ureters and kidney pelves than did the stenosis of the ureteral orifices.

CASE REPORT

Clinical history

The patient, a white male, aged 7 months, had a normal birth and was an apparently healthy baby. In his sixth month he suddenly developed a rise of temperature to 102° F. and was admitted to the hospital where a diagnosis of influenza was made. In spite of a complicating double otitis media, he made a good recovery and was discharged on the eighteenth day. No note relative to the urinary system was found.

The patient was readmitted two weeks later with the complaint of diarrhea. Physical examination showed a poorly nourished child, but was otherwise negative. No urine examination is recorded. The diarrhea disappeared within a few days, but he was retained in the hospital because of his emaciated condition. On the twelfth day his temperature rose to 103.5° F., pulse to 130, and respirations to 50 per minute. No abnormal signs were found on physical examination. He died on the fourteenth day of his stay in the hospital.

Abstract of protocol

The body is that of a markedly emaciated white boy, 59 cm. in length and weighing 3700 grams. The thymus is not enlarged. The heart is negative. The lungs show some hypostatic congestion but no pneumonia. The intraperitoneal organs are normally disposed and negative on examination.

The organs of the urinary system present a striking picture and are dissected out in toto (fig. 1). The kidneys are in their usual position and the number and course of the renal arteries show no abnormalities. The fetal lobulations are well marked. The pelves are enlarged and cystic. The ureters are dilated and tortuous, measuring from 1 to 1.5 cm. in diameter. The bladder is small, contracted, and measures 3 cm. in its external lateral diameter.

Fig. 1

Marked Hydronephrosis and Dilated Tortuous Ureters Accompany a Small Bladder in Which the Cystic Protrusions at the Site of the Ureteral Orifices Can be Seen

Note also the valve in the prostatic urethra. *a*, Left, the more detailed structure of dilated end of the ureter with the small orifice into the bladder. *b*, Right, a high power drawing of the ureteral orifice lined by stratified epithelium.

As the most frequent cause of bilateral hydronephrosis is urethral obstruction, this part of the tract is examined first. A small probe introduced into the lower urethra passes easily into the bladder. The same probe introduced from the bladder meets an obstruction about 1.5 cm. below the internal urethral orifice. With the probe in this position, the urethra is opened from below. The probe is seen to be arrested by a delicate membranous valve which extends from the lower end of the verumontanum to the right urethral wall. No such membrane can be found on the left side. The lack of dilatation in the bladder and prostatic urethra suggests that this valve is not the primary cause of the hydronephrosis.

When the small, contracted bladder is opened, very little urine is contained therein. The lining mucosa is smooth and pale. At the normal site of the ureteral orifices on each side there appears a remarkable cystic projection covered by a similar mucosa. These protrusions are about 6 mm. in diameter and from 3 to 4 mm. at their point of origin from the bladder wall. The approximated surfaces of the two protrusions are somewhat flattened. Pressure exerted upon the ureter causes these to become tense, but no urine is seen to flow from them. No ureteral orifice can be discovered by the most careful scrutiny.

In order to determine the exact point of the obstruction, X-ray photographs are taken. Through cannulae inserted into each ureter, slightly cloudy, yellow urine is withdrawn and a 10 per cent thorium solution introduced under 18 inches gravity pressure. None of the solution can be seen to pass from the protrusions, but when the specimen is examined after standing for one hour, a small amount (about 1 cc.) of the fluid is found in the bladder. The accompanying outline sketch (fig. 2) is taken from the radiographic plate. The point of ureteral passage through the bladder wall is proved to be constricted but slightly by the bladder musculature, a constriction by no means sufficient to account for the enormous dilatation of the ureters and kidney pelves. The point of obstruction must, therefore, be in the orifices themselves.

The hydronephrosis is approximately equal on the two sides. The right kidney measures 7 by 5 by 3 cm., and the left, 6.5 by 4.5 by 3 cm. On longitudinal incision the parenchyma is seen to be reduced to a thickness of from 3 to 5 mm. by the pressure of the enlarged calyces. The pyramids have assumed the shape of flattened semicircles and measure from 2 to 3 mm. in their greatest height. The striations of the cortex are almost obliterated. The lining of the pelvis is pale and smooth.

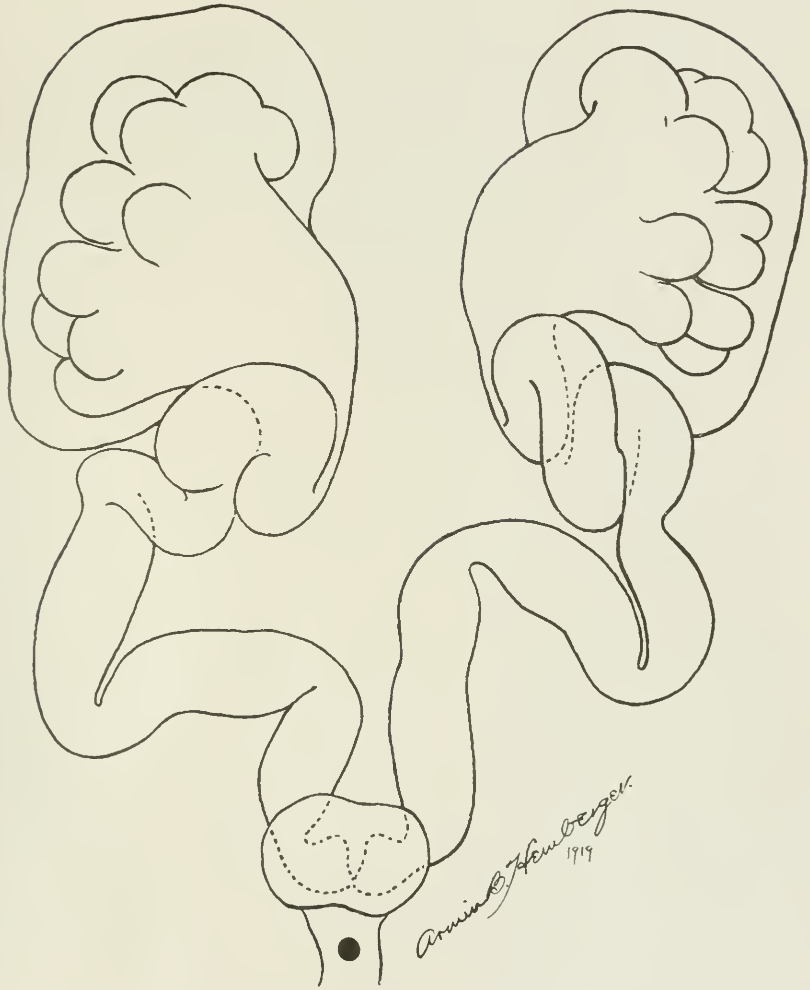


Fig. 2. An Outline Drawing from An X-ray Plate Taken After Thorium Injection of Both Ureters

Microscopic notes

Kidney. The structural changes noted in the gross examination are here also very marked. The atrophic change is found to involve the medullary somewhat more than the cortical parenchyma (fig. 3). The renal capsule is definitely thickened and the subcapsular blood vessels

Fig. 3. A Low Power Drawing of a Hydronephrotic Kidney Lobule with its Dilated Calyx

are prominent. The number of glomeruli in a given area of the cortex is apparently increased, although the individual glomeruli show little change. The epithelium of the convoluted tubules is cuboidal; their lumina are large and contain albuminoid material. Many of the collecting tubules are much dilated, showing in their flattened epithelial lining cells pronounced nuclear staining. Other tubules are so compressed by the surrounding tissues that their lumina are all but obliterated and the true nature of their distorted cells almost unrecognizable. The walls of arteries and arterioles are considerably thickened. The interstitial tissue, especially of the pyramids, is increased and infiltrated with mononuclear cells. The pelvis is lined by an epithelium which varies in different sections, or in parts of the same section, from a single layer of cuboidal or flattened cells to one of double or triple thickness.

Ureters. The walls of the ureters show hypertrophy as well as dilatation. This is evidenced in all of the muscular coats, but especially is it true of the inner circular layer. The submucous connective tissue is very scanty. The mucosa is composed of a squamous epithelium from two to four cells in thickness.

Bladder. The microscopic picture of this organ is of especial interest and importance. Both bulbous protrusions with the neighboring bladder wall are excised and serial sections cut through them in search of an opening into the vesical cavity. By this method, a tiny orifice is discovered on the inner, flattened and approximated side of each ureteral cyst (fig. 1, *a*). With sections cut at 10 micra, eleven sections include the orifice of one side, and twelve sections are required to pass through the opening of the other protrusion. The calculated width of the orifices is, therefore, from $\frac{1}{8}$ to $\frac{1}{9}$ mm. in diameter. Tissue shrinkage during the process of fixation and embedding might occur, but would probably cause no material change in size.

The walls of this cystic protrusion are somewhat thicker than the walls of the ureters above the bladder. They consist of well defined, smooth muscular coats which are continuous with the musculature of both the ureter and the bladder walls, and of a loose connective tissue submucosa in which a few mononuclear cells are seen. The lining on the inner side of the cyst is continuous with that of the ureter, and on the outer side with that of the bladder wall; the two are connected by the transitional epithelium, four or five cells in thickness, which lines the orifice (fig. 1, *b*).

No difference is found between the structure of the bladder wall around the ureterocele and that of the fundus. The muscular coats show a mild hypertrophy. The submucosa is thrown into numerous rugae and covered by four or five layers of epithelial cells in stratified form.

Urethra. Sections taken through the urethra at the level of the verumontanum and below show it to be lined by normal stratified epithelium.

Summary

A poorly nourished boy, seven months of age, was admitted to the hospital on account of diarrhea. Physical examination was negative. At autopsy there was found double hydronephrosis with dilated tortuous ureters which ended in cystic dilatations in the small vesical cavity. Grossly the ureteral orifices were not visible; by serial section they were found to be stenotic and to measure from $\frac{1}{8}$ to $\frac{1}{9}$ mm. in diameter. In addition there was present a valve extending from the lower end of the verumontanum to the right urethral wall.

VALVE IN THE PROSTATIC URETHRA

The presence of a valve formation in the lower prostatic urethra is probably the most common cause of double hydronephrosis in children. Such children not infrequently die in infancy as in the cases reported by Lowsley (21), Schlagenhaufer (26), Commandateur (9), and Jordan (17); they may reach childhood (Reports by Knox and Sprunt (18), Posner, (24), Lederer (19), and Wilckens (31)); or adult life may be attained without any indication of such a condition (Bonnet (4), Lindeman (20)).

Our knowledge of the embryologic development and the structure of this part of the genito-urinary tract is materially increased by the studies of Watson (30). In an embryo of thirteen weeks (80.3 mm.), the lower aspect of the verumontanum is found to end in three slim, elevated ridges or striae which decrease in prominence as they are traced downward and finally merge into the wall of the membranous urethra. A similar picture is observed in embryos of sixteen weeks, twenty-one weeks, thirty-one weeks, and to a lesser extent at birth. In an

embryo of the fourteenth week (105 mm.) Watson makes an extremely interesting observation, "The tip of the verumontanum in its lower third is securely attached to the roof or dorsal aspect of the urethra. The condition is apparently rare if not constituting a real anomaly, as it has not been observed in any of the other specimens studied."

It is easily conceivable that such an attachment could form the pseudodiaphragm described by Bonnet (4) and others. Those obstructions which more closely simulate valves, as in the case of Knox and Sprunt (18) and the one reported above, may have originated in the same manner or may be exaggerated remnants of the normal lateral striae.

Such an obstruction with valve formation is usually bilateral, and the urine passes only through a narrow slit. There results dilatation of the urethra above this point, dilatation and hypertrophy of the bladder, dilatation of both ureters, and double hydronephrosis. In our case, the valve was found on one side and offered only a partial interference to the passage of urine, insufficient to cause dilatation of the upper prostatic urethra and of the bladder.

CONGENITAL STENOSIS OF THE URETER

Stenosis or stricture of the ureter is a not uncommon condition and may either be due to congenital malformation or be the result of inflammatory reaction. Clinically it has been noted by Hunner, Eisendrath (10), and others. As has been pointed out by Robinson (25), cases of congenital stricture usually occur: (a) just below the pelvis of the kidney; (b) at the pelvic brim; (c) immediately above the bladder; (d) or in the wall of the bladder. Cases of stenosis or of blind ending of the ureter in the vesical wall have been collected by Schwartz (27) and Bottomley (5). Where the ureter ends blindly in the outer portion of the wall, a cystic pouch is found on the outer lateral or posterior aspect of the bladder. If the blind end is just beneath the vesical mucosa or if the orifice is stenosed, a protrusion, or ureterocele, is formed into the cavity of the bladder. For the sake of brevity, only the latter cases will be considered.

Seventeen such cases of cystic dilatation of the ureteral end with protrusion into the bladder were collected from the literature and reported by Bottomley (5) in 1910. Since then Eisendrath (12) and Buerger (6) have each added one to this number. The ages varied from fetal life to seventy-nine years, but it is noteworthy that they were at the extremes of life; ten were under sixteen years, six were over forty-eight, in two the age was not given, and Buerger (6) alone reported a clinical case in the prime of life—thirty-six years. Of these, ten were females, six males, and the sex of three is not stated. Many of the ureteroceles represented the ending of a supernumerary ureter, while the other ureteral orifices were normal in appearance. The protrusions varied from "pea size" to 6.5 cm. in length. In only one case, reported by Burckhard (7), was the condition present on both sides, and a brief abstract of this case will be given.

The patient, a male, aged sixty-two years, died of pneumonia. The ureters end at the normal site in polypoid cysts, at the apices of which are small openings into the bladder. The bladder wall at the base of these protrusions shows concentric circles with thinning of the musculature in a diameter of 1.5 cm. The ureters in their lower 5 cm. are dilated to a maximum circumference of 4.8 cm. on the right and 2.3 cm. on the left, and are again enlarged below the pelvis. The kidneys are slightly hydronephrotic. Microscopic sections through the swellings show bladder mucosa on the vesical side and ureteral mucosa on the inner side, separated by a wall of loose connective tissue and muscle. In the ureter both circular and longitudinal muscles are thickened. The explanation offered is that of a lack of development of the muscle in the bladder wall about the orifices.

In the majority of cases the protrusions were spoken of as blind, or closed; in a few, tiny openings into the bladder were noted. The criterion used to decide this point seems to have been gross examination alone. No mention is made of any attempt to look for small orifices by microscopic sections, a method which would be tedious when the cyst is several centimeters in length. Nevertheless, it is interesting to speculate as to the possibility that some may have possessed such microscopic orifices.

The explanations which have been suggested for many of these cases concern the relative position of the bladder and ureter. Bostroem (3) and Englisch (13) take the stand that the ureters in these cases do not take the normal oblique course through the bladder wall to the vesical cavity, but run for a short distance between the muscle and the mucous membrane. When the muscle contracts there is a protrusion of the end of the ureter. Burckhard (7) gives as an explanation the lack of development of the bladder muscle around the orifice. Tangl (28) and Neelson (22) seek the cause in an abnormal position of the orifice which brings it into the sphere of contraction of the internal sphincter.

None of the above explanations was tenable in this case. As is demonstrated, by the radiographic outline sketch, the passage through the bladder wall in no way obstructs the flow of urine. Nor was there found, grossly or microscopically, any difference between the amount of muscle around the orifices and that in the fundus of the bladder. The orifices were symmetrically placed and were not close enough to be affected by the action of the sphincter. In view of these facts and because of the extremely small opening demonstrated, we believe it to be a case of congenital stenosis of the orifices. This is a condition recognized clinically, as Buerger has emphasized. Pathologically it is mentioned by Carraro (8), Adrian (1), and others.

The embryological development of this area has been studied in detail by Huntington (15) and Felix (14), and has been reviewed in this connection by Schwartz (27), Johnson (16), Bottomley (5), and others. According to Felix, the ureter begins in an embryo of from 4 to 5 mm. as a bud from the primary excretory duct just above the entrance of the latter into the cloaca. Soon it comes to have a common entrance with the primary excretory duct and later is divided entirely. With the growth of the lower cloaca and the development of the bladder, the two ducts are separated, the ureter opening into the trigone, the primary excretory duct into the prostatic urethra. In an embryo of 50 mm. the lower ureter is lined by five layers of epithelial cells which at 70 mm. begins to change to the transitional type. At the same time, fine concentric muscles are seen

in the bladder about the ureteral orifice and gradually extend upward until in an embryo of 150 mm. they have reached the kidney pelvis. Whether the partial or complete closure of the orifice is due to an overgrowth of the epithelium, or the muscle, or of both cannot be determined. Otto's (23) case of a six months' fetus in which the left ureter is dilated and ends in a blind sac in that portion of the cloaca which would correspond to the bladder, is interesting in this connection.

SUMMARY

The variety of lesions makes the case reported in this article one of unusual interest. Congenital stenosis with cystic dilatation of the vesical end of one ureter is unusual, but to find this condition present to the same extent in both ureters is extremely rare. An explanation is sought in the embryological development of the ureteral orifices on the basis of which occlusion by a partial overgrowth of epithelium and muscle may be understood. A high degree of dilatation of ureters and kidney pelves follows this obstruction to the urinary flow. The combination of this double ureteral anomaly with a valve in the lower prostatic urethra is worthy of note as an example of multiple malformation of the urinary tract.

The condition offers rather complex problems in diagnosis to the clinicians. Its lack of recognition is often justifiably excused because of the extreme rarity and the indefinite symptoms. Nevertheless, because of its susceptibility to treatment, the possibility must be kept in mind.

The demonstration of orifices which are invisible without microscopic aid is often important to the pathologist. Where an insufficient clinical history offers no help, the age of the patient (seven months) immediately suggests that there must be some outlet, however small, or kidney function could not have continued to sustain life. The use of serial sections offers a valuable method of finding minute openings and of estimating their width. Whether other cases previously reported would have yielded similar results by such an examination, we can only conjecture.

REFERENCES

(1) ADRIAN: Die praktische Bedeutung der Missbildung der Niere, des Nierenbeckens und des Harnleiters. Samml. zwangl. Abhandl. ad. Geb. d. Dermat. etc. Halle, 1913–14, iii, 1–38.
(2) BAZY: Rétrécissement congénital de l'urètre chez l'homme. Presse Med., 1903, I, 215.
(3) BOSTROEM: Quoted from Burckhard.
(4) BONNET: Central. für Chirurgie, 1904, xxxi, 85.
(5) BOTTOMLEY: Certain congenital strictures of the ureters. Annals of Surgery, 1910, lii, 597–625.
(6) BUERGER: Stenosis and stricture of the ureter. N. Y. Med. J., 1917, cv, 909.
(7) BURCKHARD: Ueber Dilatation der Ureteren mit cystöser Vorwölbung ihrer Eintrittstellen in der Harnblase. Central. f. all. Path. und path. Anat. 1896, vii, 129.
(8) CARRARO: Le Stenosi congenital dell'uretere. Morgagni, Milano, e Napoli, 1917, lix, 214–242.
(9) COMMANDATEUR: Dilatation de l'appareil urinaire chez le foetus par rétrécissement valvulaire congénital de l'urètre. Lyon. Méd. 1898, Mars. 13.
(10) EISENDRATH: Congenital stenosis of the ureter. Surgery, Gynecology, and Obstetrics, 1911, xii, 533–542.
(11) EISENDRATH: Congenital malformation of the ureters. Ann. Surg., 1912, lv, 571–592.
(12) EISENDRATH: Congenital strictures and spiral twists of the ureters. Ann. Surg., 1917, lxv, 552–559.
(13) ENGLISCH: Zur pathologischen Anatomie der Harnorgane Neugeborener. Wien. Med. Wchnschr., 1911, lxi, 2339.
(14) FELIX: Development of the urogenital organs. Keibel and Mall, Human Embryology.
(15) HUNTINGTON: Harvey Lecture, N. Y., 1906–1907, 222.
(16) JOHNSON: Tr. of Path. Soc. of London, 1901, lii, 117.
(17) JORDAN: Congenital stricture of the prostatic urethra. J. A. M. A., 1913, lxi, 244.
(18) KNOX AND SPRUNT: Congenital obstruction of the posterior urethra. Tr. of Am. Ped. Soc., 1912, xxiv, 49.
(19) LEDERER: Ueber eine eingeborene membranöse Verengerung der Pars Prostatica Urethrae. Arch. f. path. Anat. und Physiol., 1911, cciii, 240.
(20) LINDEMAN: Casuistischer Beitrag zur Frage der angeborenen klappenformigen Verengerung der Pars Prostatica Urethrae. Inaug. Dis. Jena, 1904.
(21) LOWSLEY: Congenital malformation of posterior urethra. Ann. Surg., 1914, lx, 733.
(22) NEELSON: Beiträge zur path. Anatomie der Ureteren; Beiträge zur path. Anatomie und allgemeinen Pathologie, iii, 1888, 297.
(23) OTTO: Quoted from Bottomley and Schwartz.

(24) Posner: Ueber angeborene Stricturen der Harnröhre. Berl. kl. Wchnschr. 1907, xliv, 375.

(25) Robinson: Quoted from Eisendrath, S. Gyn. and Obs., 1911, xii, 533.

(26) Schlangenhaufer: Ein Beitrag. zu den angeborenen Klappenbildungen im Bereiche der Pars Prostatica Urethrae. Wien. kl. Wchnschr., 1896, xv, 268.

(27) Schwartz: Ueber abnorme Ausmündung der Ureteren und deren chirurgisch Behandlung. Beitrag zur klin. Chirurgie, 1896, xv, 159.

(28) Tangl: Beiträge zur Kenntniss der Bildungsfehler der Urogenital Organe. Virchow's Archiv, 1889, cxviii, 414.

(29) Tolmatschew: Ein Fall von semilunaren Klappen der männlichen Harnröhre und von vergrösserter Vesicula Prostatica. Arch. f. path. Anat. und Physiol., 1870, xlix, 348.

(30) Watson: The development of the human verumontanum. Bull. J. H. Hosp., 1918, xxix, 241.

(31) Wilckens: Zur Frage der kongenitalen Stenosen der männlichen Harnröhre. Zeitschr. f. Urol., 1910, iv, 814.

LYMPHO-BLASTOMA (LYMPHO-SARCOMA) OF THE PROSTATE[1]

WILLIAM C. QUINBY

From the Urological Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

In 1909, Dr. Charles L. Gibson discussed before this Society the question of sarcoma of the prostate, and at that time was able to find reports of 37 cases. Following this no comprehensive article on this subject appeared until 1917, when Parmenter was able to collect a total of 59 cases. Each of these writers grouped all forms of sarcoma together. Of the different types of tumor, the spindle celled or small round celled sarcoma were in marked majority. Sarcoma, lymphatic in its type of cell, most properly called lympho-blastoma, appears in these series of cases in only three instances. Indeed, in consideration of the fact that normally the prostatic gland contains no lymphatic tissue, it is hard to find logical source for the occurrence of this type at all.

The following case is thus the fourth of this variety of prostatic sarcoma to be recorded.

A married man of French Canadian birth, forty-one years old, a farmer, entered the Peter Bent Brigham Hospital on February 8, 1918, complaining of frequency of urination.

The family history and past history were essentially negative in all respects.

Present illness. Shortly before Christmas, 1917, the patient began to have frequency of urination with burning, more marked at the beginning and end than during the passage of the stream. At this time the urine was clear. By rest in bed under medical treatment for three or four days, the symptoms abated and the patient felt well enough to make a long railroad journey over the Christmas holiday. On reaching his destination, urinary symptoms returned more severe than before and he was compelled to enter a hospital. Here he was treated with hexamethyleneamine, hot enemata, and Sitz baths. He was told that the

[1] Read before the American Association of Genito-Urinary Surgeons, Atlantic City Meeting, June, 1919.

prostate on rectal examination was of normal size at this time but that it was inflamed. After six days he was discharged, relieved. Two days later, however, the symptoms again returned and this time he had retention of urine, necessitating catheterization. There followed five days of marked bladder difficulty, so that on the patient's return home

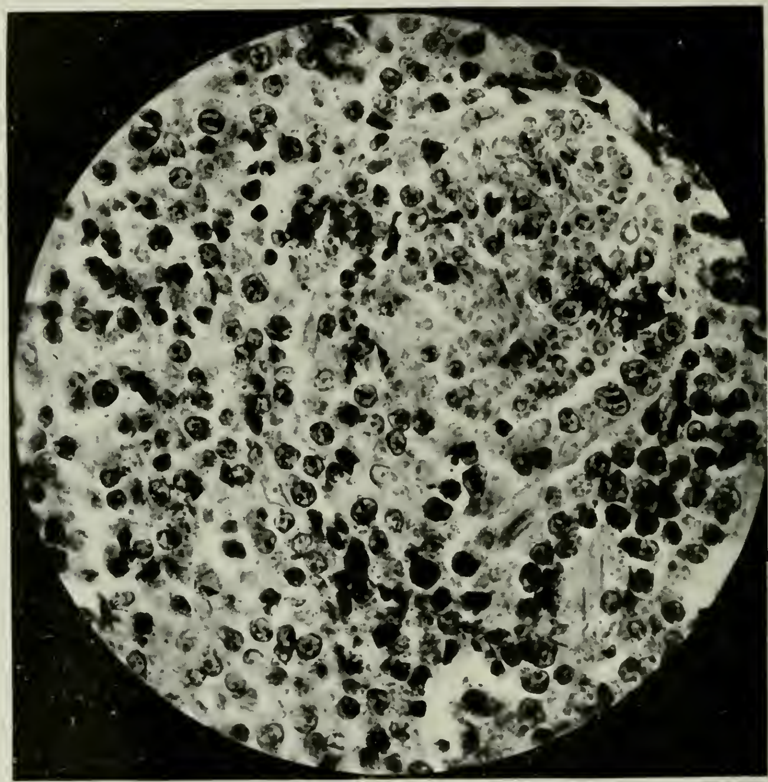


Fig. 1. Lymphoid Cells Invading a Nerve Fibre. Note Frequent Mitotic Figure

early in January, urination was as frequent as every half hour during the day and on the 20th of January this had become so great that he was having much difficulty in passing his water at all. Following severe straining, blood was passed in clots. He was given irrigations of the bladder three or four times daily, and shortly after this he experienced an epididymitis on each side, lasting about one week. A few

weeks later, on rectal examination the prostate was said to be somewhat enlarged, and there was considerable pain in the rectum. The patient was cystoscoped and a diagnosis of tumor of the prostate made. On entrance to the Brigham Hospital, the patient's appearance was good, but it was evident that he had lost a moderate amount of flesh. The urine contained much pus and a considerable amount of blood. The blood pressure was normal and the general physical examination otherwise without special significance.

At cystoscopy on February 9, the following note was made:

The cystoscope entered the bladder without obstruction but caused considerable pain. The shaft had to be depressed definitely before the tip entered, thus suggesting some enlargement in the region of the prostatic urethra. Examination of the bladder was not satisfactory on account of the amount of pain caused by the instrument. It showed, however, only a mild degree of cystitis, especially localized in the region of the trigone; no stones or tumors, no diverticula. Examination of the bladder outlet showed a number of elevations very irregular both in size and shape, and bleeding on the slightest touch. These seemed to be in the beginning of the prostatic urethra, or certainly surrounding the internal meatus, and extending into the prostatic urethra as far as could be seen with the cystoscope. The nature of these elevations was obscure. They did not seem to be pedunculated and did not suggest polyps, therefore. They seemed to be tense and as has been noted, bled on the slightest touch, so that accurate observation was practically impossible.

Rectal examination made while the instrument was in the urethra did not show any special thickening of the prostate. Rectal examination with the patient standing showed a prostate the lower two-thirds of which at least seemed to be practically normal. On reaching higher than this, however, a mass was encountered bulging toward the rectum which the patient said was very tender to touch. This seemed to be larger on the right side than on the left. On emptying the bladder, this mass disappeared. Neither seminal vesicle could be felt.

The diagnosis in this case was somewhat obscure principally on account of the difficulty encountered on cystoscopy. The story suggested an infection of the prostate accompanied at one time by a downward spreading toward the epididymis. It was not possible however to exclude tumor, in as much as Dr. Normand of Fall River on cystoscopic examination, which may have been made under more favorable circumstances than was ours, felt sure that he had found such to be present.

Operation, February 14, 1918. With the patient in the high lithotomy position, the usual incision was made connecting the tuberosities of the ischium with the bulb. After section of the recto-urethralis muscle, the rectum was pushed back and the urethra at the tip of the prostate was exposed. Here the posterior layer of the fascia was incised and the posterior retractor put in place. The long prostatic tractor had been placed previously into the bladder. Examination of the prostate and of the seminal vesicles by this route failed to demonstrate any pathology demanding surgical intervention; that is, it had been thought possible that an undrained, infected seminal vesicle might be found, but this was not the case. The wound was therefore closed after uniting the levator muscle with one chromic cat-gut stitch. The patient was then placed in the dorsal position, Trendelenberg, and the bladder opened in the usual manner above the pubes. Exploration by this route showed no tumor in the bladder, but a very vascular, easily bleeding prostatic urethra, dilated to a size easily to admit the thumb, and containing a small mass of very friable character, giving the same impression as does the liver when pinched between the thumb and forefinger. It was not to be determined whether this condition in the urethral portion of the prostate was due to chronic infection with overgrowth of the mucosa, or was due to actual neoplasm. A small bit of tissue was excised for pathologic examination and the bladder closed by interrupted sutures in the usual manner around a large drainage tube.

Pathological report. Dr. S. B. Wolbach.

Material. Tissue from prostatic urethra.

Gross description. The specimen consists of a square fragment of tissue 1 cm. square and 3 mm. in thickness, with a smaller piece 4 mm. in diameter and 1 cm. long, attached to one of the sides. The tissue is resilient and brownish. It was fixed in Zenker's fluid.

Microscopic report. The tissue is composed of a compact mass of small round cells, the size and general appearance resembling the lymphoid cells found in the germinal centers of lymph nodes. In one part of the section there are bundles of smooth muscle fibers cut in cross section, completely surrounded by this tissue. The supporting tissue consists of a delicate reticular tissue with numerous small blood vessels and capillaries. There are numerous mitotic figures and the whole appearance can only be explained on the basis of a new growth, a lympho-blastoma.

Diagnosis. Lympho-blastoma.

In view of this pathologic diagnosis, the possibility of a total prostatectomy was considered but was thought contra-indicated because of

generalized metastasis as shown by the patient's very rapid loss of weight and appetite.

On March 10, the following note was made:

The patient has gone down hill rapidly during his stay at the hospital. It is now possible to palpate a very definite tumor mass above the pubes in the region anterior to the bladder. Also there is extension to the perineum by the growth making it painful for him to sit. Yesterday he complained of pain in the left eye and on examination it was found that he was suffering from double vision. This probably means a cerebral metastasis. All the urine since operation has been passed without pain from the suprapubic opening. He is discharged to his local doctor because he very much wishes to return home and having lost strength rapidly, he will soon be unable to travel.

A letter from his physician states that death occurred about three months after operation.

It is thus seen that the early clinical picture of lympho-blastoma of the prostate in this instance was essentially that of an acute infection, and that this condition overshadowed the tumor growth which locally was only of insignificant size and interpreted only with difficulty on cystoscopic examination. Following this insidious origin, the early course and general malignancy was so great that death occurred four months after onset of symptoms.

This is so unusual and striking a picture that it will be of interest to consider in this connection the reports of the other three cases of lympho-sarcoma found in the literature.

Case of Coupland. Lymphoma (lympho-sarcoma) of the prostate; secondary nodules in pancreas and supra-renal capsules.

The patient, a police constable of twenty-nine years, married, had had one attack of gonorrhea and of chancre. The onset of his illness was three months before admission, occurring as an attack of acute retention after a debauch. He was catheterized, placed in hot bath and given opium. For the next ten days, occasional catheterization was necessary. On only one occasion was this followed by slight bleeding. Following this the patient was treated, while still in the hospital, for spasmodic stricture. The urine was thick with stringy mucus. His symptoms steadily grew worse and his strength failed rapidly. The next examination showed him to be slightly emaciated and sallow and his symptoms wholly referable to the bladder. He had a constant

desire to urinate and only a few drops of urine were passed after great straining and pain across the abdomen. There was much pus in the urine with mucus and phosphates. He complained of pain at the end of the penis. It was necessary to depress the handle of an instrument in order to make it enter the bladder. This instrument found calculous material in the bladder. Examination by rectum was very painful. It showed an almost uniformly smooth enlargement of the prostate, not very tender and of firm consistence. Two weeks later, the patient had a rigor, with fever, and pain in the lumbar region. The only symptom on the part of the rectum was a rather obstinate diarrhoea.

Death occurred fifty-four days after admission.

At autopsy the body was found to be much emaciated. There was a nodule in the pancreas at the junction of its head and body, the size of a filbert. The right adrenal was twice its normal size and was the seat of new growth. There was a bilateral pyelonephritis of severe grade. There was no dilatation of the ureters. The wall of the bladder was one-half inch thick and its cavity, no larger than a walnut, contained opaque urine. The base of the bladder was occupied by a firm mass continuous with the prostate and projecting into the bladder just below the ureters. The neck of the bladder and prostatic urethra were surrounded by tumor. The upper extremity of the growth extended into the bladder and was irregular and polypoid. The right seminal vesicle was large and swollen, the left was imbedded entirely within the tumor. The testes and epididymes were normal. There was no evident enlargement or infiltration of any of the pelvic, lumbar or inguinal lymph nodes. The rectum was empty and was not involved by the growth except through compression. The thoracic organs were normal.

Microscopic examination of the tumor showed it to be composed of small round cells in a fine meshed reticulum.

Case of Kaufmann. The patient was a color worker, twenty-five years old. In spite of the fact that there was marked enlargement of the prostate demonstrable, no clinical symptoms were caused by this.

At autopsy the prostate was found to be the size of a small fist, and was of dense consistence. The bladder was small and contained a little turbid urine. The median portion of the prostate projected into the bladder and the neck of the bladder was moderately infiltrated by a soft tumor-mass which appeared in the region of the trigone as thickened folds. The beginning of the urethra and the veru montanum were also infiltrated. The ureters were quite patent and the lumen of the urethra only a very little narrowed.

Frontal section showed the prostate to be about 6 cm. wide and 4.5 cm. high. The only normal configuration of the gland to be found appeared in the region of the left lobe. Everywhere else the tissue was replaced by a granular, white tumor-mass, which was prolonged posteriorly, especially in the region of the right seminal vesicle. The tumor was continuous into the right lobe of the prostate without any sharp line of demarcation. The seminal vesicle was converted into a mass of new growth 4 by 3 cm. without any sharp line of demarcation. On section, the tumor was white with a few yellowish brown areas and irregular furrows. The area between the ampullae of the vasa was free from tumor. There were extensive metastases in the pleura, kidneys, pancreas, dura and lymph glands of the neck, as well as in the femur, tibia, and calvarium. In the pelvis there were no glands involved except one the size of a pea, situated outside and in front of the left seminal vesicle.

On microscopic examination, the tumor and metastases both showed lympho-sarcoma; this appearing as a network of fine fibrils enclosing small spaces filled with lymphoid cells, while here and there were cells somewhat larger with multiple nuclei.

Case of Conforti and Favento. The patient was a man of forty-five years, whose illness began with a sudden attack of acute retention of urine, there having been no previous disease of the genito-urinary system. At this time the urine was clear. Examination showed the prostate to be soft and slightly enlarged. One month later, there occurred another attack with fever, severe pain in the bladder and cloudy urine. At this time, the prostate was very large, soft and fluctuating. On examination a month later, the patient was found to be having complete retention, fever and pyuria. The prostatic tumor projected into the rectum but it did not fluctuate. Transvesical prostatectomy was attempted but the growth was found already to have infiltrated the urethra and bladder. After four months illness, the patient died.

At autopsy the tumor was found to be a lympho-sarcoma, primarily of the prostate, with infiltration of the bladder, urethra and left ureter. There had occurred marked local recurrence of the tumor and this was found to occupy almost the entire space of the small pelvis and to measure about 7 by 10 cm.

From this brief contribution to the subject, it is evident that this form of tumor is highly malignant and in its early stages,

frequently difficult to diagnose. It also seems to be characteristic of this type of growth that its local symptoms are either entirely lacking or only made prominent by an intercurrent infection of the gland. The absence of infection of the local and neighboring lymph nodes seems also to be a striking feature of this type of neoplasm. In view of these facts, it is indeed fortunate that such prostatic neoplasms as these are very rare, for it is only too evident that we have no means at present, not even radium, which is adequate to control a tumor growth of such insidious origin and rapid formation of metastases.

REFERENCES

Gibson, Charles L.: Sarcoma of the prostate. Trans. Amer. Assn. of Genito-Urinary Surgeons, 1909, iv, 107.

Parmenter, F. J.: Sarcoma of the prostate. Surg. Gynec. and Obstet., 1917, xxiv, 336.

Coupland, S.: Lymphoma (lympho-sarcoma) of the prostate; secondary nodules in pancreas and supra-renal capsule. Trans. Path. Soc., London., 1877, xxviii, 179.

Kaufmann, E.: In Socin and Burckhardt. Die Verletzungen und Krankheiten der Prostata. Deutsche Chirurgie, 1902, p. 395.

Conforti, G., and Favento, P.: Il Sarcoma della Prostata. Folia Urologica, 1907–08, i, 180.

THE LIBERATION OF FORMALDEHYDE FROM AND DECOMPOSITION OF ANHYDROMETHYLENECITRIC ACID AND ITS EXCRETION IN URINE, WITH COMMENTS ON "CITARIN" AND "HELMITOL"

PAUL J. HANZLIK

From the Pharmacological Laboratory, School of Medicine, Western Reserve University, Cleveland

Received for publication January 25, 1920

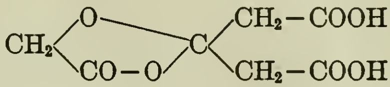
INTRODUCTION

Anhydromethylenecitric acid is of interest as a urinary, and possibly as an intestinal, antiseptic because of the possibility of liberating formaldehyde from it in alkaline media. The opposite of this is hexamethyleneamine, which liberates formaldehyde in fluids possessing a truly acid reaction, i.e., for practical purposes, in acid urine only. By means of these two compounds, therefore, it might appear that the antiseptic armamentarium would be able to meet all the exigencies pertinent to the variabilities in chemical reactions of body fluids. The mechanism of action of hexamethyleneamine is well established. Concerning the exact behavior of anhydromethylenecitric acid practically nothing is known, although it has formed the basis of two other products, namely its sodium salt ("citarin") and the hexamethyleneamine anhydromethylenecitrate ("helmitol"), which have been extolled as efficient urinary antiseptics, particularly "helmitol." As far as I am able to ascertain there are only the few and uncritical experiments by Impens (1) on the excretion in urine of man, and, on blood pressure effects in cats. The advantages that "helmitol" is alleged to possess over hexamethyleneamine are ascribed to its anhydromethylenecitric acid component. Obviously, such claims in the absence of definite knowledge concerning the behavior of anhydromethylenecitric acid are pure

speculation and unjustified. Therefore, it seemed appropriate to investigate the behavior of anhydromethylenecitric acid.

The experiments were planned to determine mainly the exact degree of alkalinity under which liberation of formaldehyde occurs; the decomposition of anhydromethylenecitric acid; its excretion in urine; liberation of formaldehyde in ammoniacal urine and preservation of urine. A few subsidiary points were also elucidated. Before proceeding to the results a brief description of anhydromethylenecitric acid is desirable.

Description. Anhydromethylenecitric acid is a white, crystalline solid of rather strong acid taste; melting point, 208°. Its solubility is relatively slow in water and acids, more rapid in alkalies with the liberation of formaldehyde. Its empirical formula is $C_7H_8O_7$ and the structural formula is given by Percy May (2) and by Abderhalden in the Biochemisches Handlexikon (3) as



According to this the molecular weight is 204. The acid is prepared by heating citric acid with paraformaldehyde, or by the action of chlormethyl alcohol ($Cl.CH_2OH$) on citric acid at 130° to 140° in which case a better yield is obtained.

METHODS

These will be described under the various headings throughout the text.

RESULTS

Solubility. As indicated by titration with decinormal bicarbonate and hydroxide, using methyl red and methyl orange as indicators, the limit of solubility for anhydromethylenecitric acid in water at room temperature is about 2.3 per cent. One per cent of acid dissolves slowly and completely with shaking. This is somewhat facilitated by warming, but a high degree of heat must be avoided, since this will liberate formaldehyde. Such solutions would give false results when used for testing as

to liberation of formaldehyde. The acid is soluble in alcohol and ether; more freely in alkalies than water and not so readily in dilute acids.

As far as solubility is concerned it appears that anhydromethylenecitric acid could be relatively easily absorbed from the alimentary tract.

Total acidity. One-hundredth gram of anhydromethylenecitric acid (i.e., 1 cc. of 1 per cent in water) was found to require 1.04 cc. of $\frac{N}{10}$ NaOH (= to 1.03 cc. $\frac{N}{10}$ HCl) or $\frac{N}{10}$ $NaHCO_3$, using methyl red and methyl orange as indicators. That is, 0.01 gram of the acid requires about 0.0043 gram of NaOH or 0.0089 gram of $NaHCO_3$ for neutralization. One-hundredth gram of the acid was found to require 0.00502 gram $(NH_4)_2CO_3$ for neutralization. Whether the concentrations of alkaline salts represented by these solutions would suffice for the liberation of formaldehyde is another question. This would depend on the degree of alkalinity, i.e., hydroxyl ion concentration rather than the concentration of the alkaline salts. This will be considered later. The concentration of bicarbonate (0.6 per cent) necessary for neutralization of 1 per cent anhydromethylenecitric acid may occur in intestinal juice. Since no demonstrable formaldehyde is liberated at neutrality, it is entirely conceivable that the anhydromethylenecitrate is absorbed as such from the alimentary tract without decomposition. This proved to be the case, in part at least, as indicated by the data to be referred to later.

Free acidity. Anhydromethylenecitric acid possesses a rather strong acid taste, although as compared with strong mineral acids, it is a relatively weak acid. The hydrogen ion concentration of a 1 per cent solution was found to be about pH 2.4, using methyl violet as an indicator, or, in other words, the acidity of about a normal ($\frac{N}{1}$) solution of acetic acid. This is much weaker than the acidity of $\frac{N}{10}$ HCl, which gives a pH of about 1.0.

Accordingly, anhydromethylenecitric acid should be rather irritating particularly if used in large doses.

Free and total acidity of "helmitol." "Helmitol" possesses a distinctly acid taste, which is lost when the drug is completely neutralized by hexamethyleneamine. The hydrogen ion concen-

tration of a 1 per cent solution was found to be somewhat weaker than that of anhydromethylenecitric acid, namely, between pH 3.8 and 4.0, using methyl violet as an indicator.

One-hundredth gram of "helmitol" was found to require 0.4 cc. of $\frac{N}{10}$ sodium hydroxide for neutralization or about 0.4 of that for a corresponding quantity of anhydromethylenecitric acid. In other words, 1 part of "helmitol" appears to contain about 0.4 part, or roughly one-half, of anhydromethylenecitric acid. Since anhydromethylenecitric acid possesses 2 carboxyl groups, it would appear that "helmitol" is only about half neutralized by the base, hexamethyleneamine. This would make it an acid salt.

However, actual titration with hexamethyleneamine using different indicators gives peculiar results. Using methyl red as an indicator, it was found that about 0.086 to 0.09 gram of hexamethyleneamine is necessary for the neutralization of 0.01 gram of anhydromethylenecitric acid. Theoretically, 0.01 gram of anhydromethylenecitric acid should require 0.0137 gram of hexamethyleneamine, providing both hydrogen atoms of the 2 carboxyl groups are replaced by hexamethyleneamine. The quantity found necessary by me was about six times the theoretical. Using methyl orange as an indicator, the same quantity (0.01 gram) of anhydromethylenecitric acid required only 0.013 gram hexamethyleneamine, which is equivalent to 100 per cent of theory, but the solution was still acid to methyl red, and phenolsulphonephthalein. That is, complete neutrality is not attained when methyl orange is used. With congo red as an indicator, the same quantity (0.01 gram) of the acid required 0.025 gram of hexamethyleneamine, which is again too high as compared with the theoretic requirement. "Helmitol" itself is acid to congo red. In these titrations considerable difficulty was experienced in recognizing the end-points, particularly with methyl red and congo red. Therefore, it is probable that under these conditions it is impossible to arrive accurately at the neutralizing power of hexamethyleneamine. It is interesting to note that the solutions titrated with hexamethyleneamine, using methyl red and congo red as indicators, did not possess an acid

taste, but were rather salty, and later slightly sweetish. On the other hand, "helmitol," which is said to be a definite chemical compound of hexamethyleneamine and anhydromethylenecitric acid, and the titrations in which methyl orange was used, tasted strongly acid. Anhydromethylenecitric acid completely neutralized by sodium hydroxide also did not possess an acid taste.

The results indicate that "helmitol" is an imperfectly neutralized anhydromethylenecitric acid (by hexamethyleneamine). This phase of the study was not pursued further in view of the results which later established the worthlessness of anhydromethylenecitric acid as an antiseptic.

Changes in true reaction (pH) attained by the addition of different alkalies to anhydromethylenecitric acid. When anhydromethylenecitric acid is neutralized by titration with bicarbonate and hydroxide, using methyl red and methyl orange as indicators, it is still acid toward phenolsulphonephthalein. It appeared probable that the liberation of formaldehyde from anhydromethylenecitric acid depends on a definite degree of alkalinity. From the fact that alkali is consumed in neutralization, it was necessary to ascertain the magnitude of changes in pH obtainable by the addition of alkalies. This was done colorimetrically with phenolsulphonephthalein. Decinormal alkalies (hydroxide, bicarbonate and ammonium carbonate) and phosphate "buffer" mixtures were used. These were added gradually to 0.01 gram of anhydromethylenecitric acid (1 cc. of 1 per cent) adding phenolsulphonephthalein as indicator and comparing the final mixtures with a series of standard phosphate mixtures and alkalies ranging from pH 6.4 to 14.07. It was endeavored to ascertain how much alkali was necessary to bring about an end-reaction approaching that which occurs in alkaline body fluids, such as intestinal juice and blood, and that attainable in urine after the administration of alkali. These data were intended to be used for the determination of the exact level of pH at which formaldehyde is liberated from anhydromethylenecitric acid. This will be discussed later. For the present it may be stated that the level of alkalinity at which liberation occurs was found to be rather high. The data which are presented in table 1,

indicate that anhydromethylenecitric acid requires considerable alkali before neutrality and true alkalinity are reached.

If liberation of formaldehyde can not occur until true alkalinity is reached, it is apparent that a higher concentration of alkaline salts than can occur in such fluids as intestinal juice and urine, perhaps even fermented or ammoniacal urine, is necessary. It

TABLE 1

Quantities of different alkalis necessary to produce different changes in pH *of 0.01 gram of anhydromethylenecitric acid (1 cc. of 1 per cent)*

$\frac{N}{10}$ $NaHCO_3$		$\frac{N}{10}$ NaOH		$(NH_4)_2CO_3$ 0.68N		"BUFFER" PHOSPHATE MIXTURES	
						pH of phosphate mixture used	End pH of phosphate and anhydromethylene citric acid mixture
cc.	*pH*	*cc.*	*pH*	*cc.*	*pH*		
1.05	6.5	1.05	6.5	1.65	<6.4	7.6	7.0
2.7	7.0	1.11	7.5	2.5	6.6	7.7	7.1
3.0	7.2	1.20	>8.4	2.6	7.0	7.8	7.1
3.12	7.4	2.00	13.07	2.65	7.1	8.0	7.2
3.25	7.6			2.7	7.2	8.2	7.3
3.5	7.8			2.8	7.4	8.4	7.4
3.6	8.3 (?)			2.95	7.5		
3.82	8.4 (?)			3.0	7.7		
12.00	8.2 or 8.3			3.85	7.8		
18.00	8.3 or 8.2			4.3	8.0		
				4.85	8.2		
				4.65	<8.2		
				>7.0	8.4 (Could not be reached)		

would mean that the alkalinity of intestinal juice would have to be higher than it is naturally in order to decompose the acid with the liberation of formaldehyde and prevent its absorption as such. The data indicate that anhydromethylenecitric acid is probably absorbed as such from the intestine without decomposition. Decomposition, of course, may occur later in the circulation and tissues. This was found to be the case as will be shown later.

If anhydromethylenecitric acid is to exhibit its alleged antiseptic properties as a result of the liberated formaldehyde in alkaline urine, the data obtained indicate that the alkalinity necessary for this would have to be higher than is probably attainable. This already speaks against the compound as a urinary antiseptic.

Application of tests for formaldehyde liberated from anhydromethylenecitric acid. In attempting to ascertain the exact degree of alkalinity (as judged by changes in hydrogen ion concentration) necessary for the liberation of formaldehyde from anhydromethylenecitric acid, it is obvious that tests which require a high degree of hydroxyl ion concentration are precluded. This is true of both the phloroglucin and phenylhydrazin-nitro-prusside tests. That is, these tests cannot be applied directly to the agent, since the alkalinity, which is necessary for positive reactions with formaldehyde, is high enough to decompose the anhydromethylenecitric acid. Phloroglucin was found to require a pH of 12.13 before a positive test can be obtained with 1:100 formaldehyde, its sensitivity of course, being at least 10,000 times as great with proper alkalinity. This degree of alkalinity corresponds to the alkalinity of a solution of 0.01 N sodium hydroxide.

The same holds true of the application of the phloroglucin test in studying the relation of degree of acidity to formaldehyde liberation. This is different with a formaldehyde compound like hexamethyleneamine, which is not decomposed even in high degrees of alkalinity. Here the phloroglucin is the test of choice, those requiring an acid reaction being prohibited. If anhydromethylenecitric acid were not decomposable in acid media, certain of the formaldehyde tests performed under conditions of acidity might be used. However, all of these, except Denigé's test (5) require a high degree of acidity (concentrated acid) which is sufficient to decompose the anhydromethylenecitric acid. Denigé's reaction was found to possess a low degree of sensitivity, and to react positively with alkalies alone in the absence of formaldehyde. It was, therefore, necessary to adopt a different procedure for the exact study of the relationship of

true chemical reaction to liberation of formaldehyde from anhydromethylenecitric acid than by direct application of various tests. It follows from what has been said about the phloroglucin and similar tests that any conclusions that may be drawn concerning the liberation of formaldehyde from anhydromethylenecitric acid in vitro and in urine without due regard for the proper conditions of applying the test are erroneous and unjustified. Such appears to be the case in the work of Impens who made a few observations on the liberation of formaldehyde in vitro, and excretion of anhydromethylenecitric acid in urine. As far as I know no other work on this compound has been reported to date. The experiments on the liberation of formaldehyde may now be described.

Liberation of formaldehyde from anhydromethylenecitric acid according to different degrees of alkalinity (pH). This was determined by aeration of mixtures of "buffer" phosphate solutions, alkalies of definite hydrogen ion concentration and definite quantities of anhydromethylenecitric acid. Owing to the acidity of anhydromethylenecitric acid, the pH values of the final mixtures were different from the original solutions of known hydrogen ion concentrations, unless the acid was previously neutralized. Both methods were practised. That is, one series of solutions was made up by direct addition of solutions of known pH values, and in another series the anhydromethylenecitric acid was first neutralized with sodium hydroxide or bicarbonate. The quantities of these necessary was indicated in the first part of the paper. In both series of experiments the pH values of the final mixtures were confirmed by matching against standards of the same salts used in making up the solutions of known pH values and the same dyes. Phenolsulphonephthalein was used for the range from pH 6.4 to 8.4, cresolphthalein for the range from 8.3 to 9.6, and phenolphthalein for 8.9 to 14, using in each case 0.5 cc. of the solution of the dye (usually 1 per cent in alcohol) to 10 cc. of the final mixture, and also in the standards.

The final mixtures containing the anhydromethylenecitric acid were allowed to stand for ten minutes as a rule; in some cases as high as thirty minutes, in order to allow sufficient time

for the decomposition in doubtful cases. These were then aerated rapidly for twenty to thirty minutes into 10 cc. of 0.4 per cent ammonia water using long test tubes (20 by 180 mm.) for both the ammonia water and the final mixtures.

After aeration was completed, the ammoniated water, which now also contained hexamethyleneamine, providing formaldehyde was liberated in the mixtures, was directly acidified in the long test tube with 10 per cent sulphuric acid, heated to the boiling point to liberate free formaldehyde and cooled in running water. The phloroglucin test was now applied. As a rule 0.5 cc. of 1 per cent phloroglucin [reagent (Merck)] in 10 per cent sodium hydroxide was used to 10 cc. of solution. If the test was positive, this showed the liberation of free formaldehyde under the conditions of the mixtures containing anhydromethylenecitric acid in solutions of known hydrogen ion concentration.

By this method it is possible to detect the presence of 1:1,000,000 of absolute formaldehyde in the solution being aerated. Numerous experiments with formaldehyde in water were made to determine the limit of sensitivity of this method. Solutions of 1:1,000,000 gave definite tests, so the limit of sensitivity is probably even less, though not 1:10,000,000, which gave negative results. It seemed best to adhere to the concentration of 1:1,000,000, which was regarded low enough for the purpose. That is, the concentration of formaldehyde existing in the mixtures described above must be of no practical importance in the absence of positive tests for formaldehyde, when 0.01 gram of anhydromethylenecitric acid theoretically and by experiment yields about 0.00147 gram formaldehyde in 10 to 20 cc. of solution, or about 1:6800 to 1:13,000 concentrations of formaldehyde, respectively. In the majority of my experiments 1 cc. of 1 per cent (0.01 gram) anhydromethylenecitric acid was used in 10 cc., 20 cc. in some, and in others 2 cc. of 1 per cent (0.02 gram) in 20 cc. were used. This will be indicated in table 2, which contains data pertinent to the liberation of formaldehyde according to different degrees of alkalinity.

The results in table 2 were confirmed in the following way: It will be recalled that phloroglucin reacts positively (producing

a red color) with formaldehyde at a degree of alkalinity corresponding to pH 12.13, but not at pH 12.12. That is, the alkalinity required is at least that of a centinormal ($\frac{N}{100}$) sodium hydroxide solution. Mixtures of anhydromethylenecitric acid and sodium hydroxide were made up to correspond to the values of pH 12.12, 12.13, 13.07 and 14.05 as in table 2 and to each of

TABLE 2

Liberation of formaldehyde from anhydromethylenecitric acid according to different degrees of alkalinity

pH SOLUTIONS USED AND QUANTITY	ABSOLUTE QUANTITY OF ANHYDROMETHYLENE CITRIC ACID USED	pH OF FINAL MIXTURES	FREE FORMALDEHYDE (− = ABSENT + = PRESENT)
	gram		
18 cc. Phos.* = 8.4	0.02	7.4	−
18 cc. $\frac{N}{10}$ $NaHCO_3$ = 8.2	0.02	8.2	−
2 cc. $\frac{N}{10}$ NaOH to neutralize, then 20 cc. $\frac{N}{10}$ NaOH = 12.12	0.02	8.4	−
2 cc. $\frac{N}{10}$ NaOH to neutralize, then 10 cc. Phos. = 8.4	0.02	8.4	−
2 cc. $\frac{N}{10}$ NaOH to neutralize, then 10 cc. $\frac{N}{100}$ NaOH = 12.13	0.02	12.13	−
2 cc. $\frac{N}{10}$ NaOH to neutralize, then 10 cc. $\frac{N}{10}$ NaOH = 13.07	0.02	13.07	+ (Equal to a concentration of formaldehyde of less than 1:1,000,000 and more than 1:10,000,000; just positive)
2 cc. $\frac{N}{10}$ NaOH to neutralize, then 10 cc. $\frac{N}{10}$ NaOH = 14.05	0.02	14.05	+ (Very Strong)

* Phos. refers to mixtures of Na_2HPO_4 and NaH_2PO_4 made up to obtain pH values in the usual way.

these 0.5 cc. of 1 per cent phloroglucin in alcohol was added. The results were as follows: yellowish color or negative for formaldehyde in the mixtures with pH values of 12.12 and 12.13; reddish or just positive in pH 13.07 and deep red or strongly positive in pH 14.05. The theoretical yield of formaldehyde in these mixtures was equivalent to a concentration of about

1:4800, yet in the mixture of pH 12.13 in which the phloroglucin is readily positive with a concentration of 1:10,000 and even less, formaldehyde was not demonstrable by direct testing or by aeration.

Since, it is known that a concentration of formaldehyde of 1:1,000,000 is readily recognizable by means of the phloroglucin test, the limit being about 1:10,000,000, it is obvious that whatever concentration might be present in the mixture of pH 12.13 must be negligible for all practical purposes. The phloroglucin test with the mixture of pH 13.07 was just about positive, indicating that this is about the lowest limit of alkalinity at which liberation of formaldehyde occurs. These tests were performed at room temperature. It is possible that a temperature equivalent to body heat might facilitate the decomposition so as to bring the limit of alkalinity below pH 13.07.

Therefore, another set of tests was performed with mixtures of anhydromethylenecitric acid and sodium hydroxide ranging from pH values of 12.12 to 14.05, as in table 2. These were then incubated for fifteen to twenty minutes at 40°C. in a water bath, and then 0.5 cc. of 1 per cent phloroglucin in alcohol was applied to each tube. The limit for the positive test was precisely the same as when the same experiment was performed in the cold as described above. That is, formaldehyde was absent in the mixtures of pH 12.12 and 12.13 and present in mixtures of pH 13.07 and 14.05. The colors differed quantitatively only, being considerably deeper in the incubated tubes than in the cold solutions, indicating that the liberation of formaldehyde from, or, in other words, the decomposition of, anhydromethylenecitric acid is greatly accelerated with increase in temperature. Later it will be shown that longer heating at the boiling point decomposes almost all of it. Aside from this, the results thus far presented indicate that it is the degree of alkalinity, i.e., the hydroxyl ion concentration, which is of the greatest importance for the liberation of formaldehyde from anhydromethylenecitric acid.

It is, of course, highly improbable that such a degree of alkalinity as pH 13.08, corresponding to the alkalinity of a deci-

normal ($\frac{N}{10}$) sodium hydroxide solution can ever be attained in the living organism. The following fluids must be considered in this connection, namely, pancreatic or intestinal juice, blood, urine and fermented or ammoniacal urine. There is plenty of evidence to indicate that intestinal juice is variable, being either very slightly alkaline [the alkalinity of $\frac{N}{70,000}$ K(OH) (Foa) (5)], very slightly acid or neutral [pH 5.6 to 6.6 (McLendon, Shedlov and Karfan) (6)] in animals, and probably usually slightly alkaline in man. Since its alkalinity is due chiefly to sodium bicarbonate whose pH value in high and low concentrations ($\frac{N}{10}$ to 2 to 3 per cent) is about pH 8.2 or 8.3, it is apparent that no formaldehyde can be liberated in the alimentary tract. The limit of alkalinity (pH value) of the blood is about 7.4. The highest alkalinity attainable in urine after the administration of very large doses (40 grams) of sodium bicarbonate gives pH values of 8.7 (Henderson and Palmer (7)). This practically corresponds to the excretion of a solution of about a one-hundredth normal ($\frac{N}{100}$) disodium phosphate (Na_2HPO_4). Therefore, we may exclude intestinal juice, blood and urine (rendered alkaline in normal individuals) from the possiblities in which liberation of formaldehyde may occur. This leaves ammoniacal or fermenting urine in the bladder.

The almost total lack of data in the literature on the degrees of alkalinity attainable in fermenting urines leaves very little for consideration along this line. However, it is practically certain that no such degree of alkalinity as corresponds to that of a $\frac{N}{10}$ sodium hydroxide equal to the lowest pH (13.07) necessary for liberation of formaldehyde is ever attained in the bladder. It is a well known fact that ammonia in the form of carbonate or hydroxide in aqueous solutions can not attain this degree of alkalinity. For instance, $\frac{N}{100}$ NH_4OH has the value of pH 10.77 and $\frac{N}{1}$ NH_4OH of pH 11.77 (L. Michaelis (8)), all of these representing concentrations of hydroxyl ions (alkalinity) less than necessary for the lowest limit (pH 13.07) at which anhydromethylenecitric acid begins to liberate formaldehyde. Furthermore, bearing in mind the mutual avidity of these compounds, free formaldehyde cannot exist in the presence of ammonia.

Quantitative methods for estimating ammonia and formaldehyde based on this principle are well known, and I have shown in this paper that formaldehyde can be volatilized by aeration from as weak a solution as 1 : 1,000,000 and caught in dilute (0.4 per cent) ammonia water.

These deductions and evidences are against anhydromethyenecitric acid occupying a serious position among urinary antiseptics. Even though it should be excreted unchanged in the urine, it is inconceivable that free formaldehyde would be liberated from it in the bladder. This was tested out and the evidences, which were obtained, fully confirm the deductions and conclusions reached above, even for highly ammoniacal urines. Before proceeding to this, it will be of interest to submit the results obtained on the effects of acidity on anhydromethylenecitric acid and its destruction in vitro.

Liberation of formaldehyde from anhydromethylenecitric acid according to different degrees of acidity (pH). This is of interest in connection with the liberation of formaldehyde in gastric juice and acid urine, although it is fairly well known that the decomposition of the compound does not proceed as readily in acid as in alkaline media. Mixtures of anhydromethylenecitric acid and hydrochloric acid of known hydrogen ion concentrations were made, aerated into ammonia water and the ammonia water was then tested with phloroglucin in alkali after appropriate treatment as described in the early part of the paper. The results were entirely negative for liberated formaldehyde in the following solutions with their pH values of the final mixtures; $\frac{N}{100}$ HCl (pH 3.4), $\frac{N}{10}$ HCl (pH 1.2), $\frac{N}{1}$ HCl (pH more than 0.1 and less than 1.0). The pH values of the final mixtures were necessarily greater, indicating weaker acidity, than those of the original strengths of hydrochloric acid, since anhydromethylenecitric acid is itself a rather weak acid, acting as a "buffer." It is plain from these data that no liberation of formaldehyde could occur in any of the acid fluids of the body, since these are much weaker than the concentrations of hydrochloric acid tried. When a solution of anhydromethylenecitric acid is layered on concentrated sulphuric acid containing phenol (Liebermann's

test), a red color develops, indicating the presence of liberated formaldehyde.

Destruction of anhydromethylenecitric acid in vitro. Theoretically, the formaldehyde content of anhydromethylenecitric acid is about 14.7 per cent. This was substantiated by direct analysis. The formaldehyde was estimated quantitatively by the colorimetric method of Hanzlik and Collins (9) previously described. One cubic centimeter of 1 per cent (0.01 gram) anhydromethylenecitric acid was made strongly alkaline with 1 cc. of 20 per cent sodium hydroxide and partly diluted with water. To this was added 1 cc. of phloroglucin in alkali and the whole was diluted to 50 cc. in a short Nessler tube; and compared with a series of standards of congo red and methyl orange representing different concentrations of formaldehyde as directed in the method. The solution matched a concentration of 1:35,000 or about 0.003 per cent, which on calculation is the equivalent of 0.0015 gram of absolute formaldehyde or about 102 per cent of theory (0.00147 gram). Results varying from 98 to 102 per cent were obtained.

The results were quite different when 0.01 gram of anhydromethylenecitric acid was boiled and distilled with alkali. The formaldehyde content of the distillate was estimated also colorimetrically, but the recoveries in two different trials were 0.0006 gram and 0.00089 gram, or about 41 per cent and 62 per cent, respectively. The residues left behind after distillation was completed were free from formaldehyde as indicated by negative tests with phloroglucin. These results indicate considerable destruction of the anhydromethylenecitric acid. What happens to the formaldehyde was not ascertained. It may be oxidized to formic acid or polymerized, being converted into the para form $(CH_2O)_n$ or formose $(CH_2O)_6$. Presumably it is oxidized, since treatment of formaldehyde solutions with alkali hydroxides is known to transform formaldehyde into formic acid and methyl alcohol (Richter-Spielmann: Organic Chemistry, vol. i, 1919, p. 198), while distillation of aqueous solutions of formaldehyde or hexamethyleneamine alone yields 98 to 100 per cent recoveries.

Weak aqueous solutions of anhydromethylenecitric acid gradually liberated formaldehyde on standing. That is, decomposition of the acid is continuous and this is accelerated by heat and alkalies. The decomposition in water was repeatedly shown by simple aeration of standing solutions into ammoniated water and testing for formaldehyde in the usual way. Precaution was exercised, therefore, by using freshly prepared solutions in all experiments performed with the compound. The longer the solutions stood the more formaldehyde was detectable. Incubation of aqueous solutions alone facilitated the liberation of formaldehyde. While even a high degree of acidity in the cold did not liberate formaldehyde, incubation at 37.5°C. with the same degrees of acidity (pH 0.1 and 1.0) yielded formaldehyde definitely.

The decomposition with liberation of formaldehyde appears to be a reversible reaction, as illustrated by the following equation:

$$\underbrace{HOOC(OH)C\left\langle\begin{array}{l}CH_2\cdot COOH\\ CH_2\cdot COOH\end{array}\right.}_{\text{citric acid}} + \underbrace{(CH_2O)_n}_{\text{paraformaldehyde}} \rightleftarrows \underbrace{OOC\cdot(CH_2O)\cdot C\left\langle\begin{array}{l}CH_2\cdot COOH\\ CH_2\cdot COOH\end{array}\right.}_{\text{anhydromethylenecitric acid}} + \underbrace{H(OH)}_{\text{water or alkali}}$$

Having ascertained sufficiently the behavior of anhydromethylenecitric acid physically and chemically, we may now proceed to the experiments on excretion. From what was observed in vitro, it was anticipated that these would be entirely negative so far as liberation of formaldehyde in urine is concerned. The quantitative excretion was also expected to be small. However, it was deemed necessary to supply actual data in this direction because of the claims that are made by Impens (1) for anhydromethylenecitric acid, and by the manufacturers for "helmitol."

Excretion of anhydromethylenecitrate and liberation of formaldehyde in urine. Two experiments were performed. On two different occasions subject P. J. H. took 1 gram of anhydromethylenecitric acid, once with and once without alkali. Urine was collected at end of fifteen minutes, one-half hour and at end of

each hour thereafter until the excretion ceased as indicated by the phloroglucin test applied to a specimen of urine previously raised to the boiling point with 5 to 10 per cent sodium hydroxide. Each specimen of urine was carefully measured, and the excretion of the citrate determined quantitatively by the colorimetric method for formaldehyde previously described by Hanzlik and Collins (9). The hydrogen ion concentrations (pH values) of the urines were also determined colorimetrically in the usual way. The urines were analyzed immediately after voiding. They were also aerated for free formaldehyde as described in the fore part of the paper. The results of the two experiments are presented in the following protocols.

Experiment 1

At 12.05 a.m.

Subject P. J. H. took by mouth 1 gm. anhydromethylenecitric acid

NUMBER OF URINE SPECIMEN	PERIOD (END OF)	VOLUME VOIDED	REACTION TO LITMUS	ANHYDROMETHYLENECITRIC ACID (+ = PRESENT)	QUANTITY OF ANHYDROMETHYLENECITRIC ACID EXCRETED—EXPRESSED AS GRAM HCHO	FREE FORMALDEHYDE (BY AERATION) (— = NONE)
	hours	*cc.*				
1	¼	30	Acid	+ (Weak)	0.00003	—
2	½	65	Acid	+ (Definite)	0.00033	—
3	1	290	Acid	+ (Strong)	0.00235	—
4	2	240	Acid	+ (Strong)	0.00240	—
5	3	50	Acid	+ (Less strong)	0.00063	—
6	4	30	Acid	+ (Weak)	0.00038	—
7	5	40	Acid	+ (?)	0.00003	—
Total excreted......................................					0.0064 or 4.4 per cent	

It is seen that the excretion begins rather promptly, the compound being detectable in urine in fifteen minutes after administration. This was anticipated because of its fairly good solubility in alkalies as indicated in the fore part of the paper. The excretion appears to reach its maximum at the end of about one hour and is practically completed at the end of five to six hours. This, of course, would depend on the diuresis, which in these experiments was maintained at a fairly high level by liberal

ingestion of water. Free formaldehyde was absent in all specimens of both experiments, even in the alkaline series (experiment 2). This would be expected, since the alkalinity was not high enough for liberation of formaldehyde. It will be recalled that an alkalinity of about pH 13.07 is necessary for this.

Experiment 2

One hour previously Subject P. J. H. took by mouth 10 grams sodium bicarbonate; at 10.35 a.m., took 1 gram anhydromethylenecitric acid, and one hour after this, 5 grams of bicarbonate to maintain urine alkaline

NUMBER OF URINE SPECIMEN	PERIOD (END OF)	VOLUME OF URINE VOIDED	REACTION (pH)	ANHYDROMETHYLENE CITRIC ACID (+ = PRESENT)	QUANTITY OF ANHYDRO-METHYLENE CITRIC ACID EXCRETED-EXPRESSED AS GRAM HCHO	FREE FORMALDEHYDE (BY AERATION) (− = NONE)
	hours	*cc.*				
1	$\frac{1}{4}$	255	7.9	+ (Weak)		−
2	$\frac{1}{2}$	210	7.6	+ (Definite)	0.00053	−
3	1	290	7.4	+ (Strong)	0.00300	−
4	2	320	7.7	+ (Strong)	0.00160	−
5	3	100	7.9	+ (Strong)	0.00050	−
6	4	80	8.0	+ (Less strong)	0.00080	−
7	5	50	7.9	+	0.00063	−
8	6	40	7.8	+ (?)		−
Total excreted......................................					0.00710 or 4.6 per cent	

There is no doubt that anhydromethylenecitric acid is present as such in the urine. Direct application of the phloroglucin test in alkali without previous heating gave, as a rule, practically no color, except with the very concentrated urines. However, when the urines were previously raised to the boiling point with a little 20 per cent alkali and then the phloroglucin test was applied, there was an immediate development of red color, this being very deep with the more concentrated urines. This means that the formaldehyde is in combined form, in other words, as anhydromethylenecitrate, which requires decomposition by alkali as in pure aqueous solution before the formaldehyde is liberated. As indicated by the results of both experiments, the quantity of anhydromethylenecitrate excreted is very small (4.4 and 4.6 per cent), indicating that the compound is almost entirely

destroyed in its passage through the body. The feces were not examined, but its solubility and rapid excretion indicate that it is completely absorbed just as hexamethyleneamine is. It was previously observed with similar dosage that about 80 per cent of hexamethyleneamine is excreted in urine. No disturbances of the alimentary tract such as nausea, vomiting and diarrhea were experienced after anhydromethylenecitric acid.

As to the nature of the destruction it is suggested that the citric acid portion of the molecule is oxidized just as ordinary citric acid is, a portion of the compound escaping because of the rapid excretion. The formaldehyde portion is presumably oxidized to formic acid as usual. There are no data for deciding whether the oxidation of the formaldehyde radical occurs before or after that of the citric radical.

The results on excretion are confirmative of the tendency of the behavior of anhydromethylenecitric acid in vitro. It was found to be quite readily destroyed with moderately prolonged heating and alkali and distillation. The results indicate that the compound could not be excreted in sufficient concentration to impart especially valuable antiseptic qualities to urine. It certainly could not surpass hexamethyleneamine, even for alkaline urines, whose alkalinity can be altered by means of diuresis and administration of acids or acid salts. Greater difficulties are, of course, encountered with the antisepsis of strongly ammoniacal or decomposing urines, as in cystitis. It is alleged that "helmitol" (hexamethyleneamine anhydromethylenecitrate) is superior to hexamethyleneamine in this condition. The advantage, it is claimed, depends on the property of "helmitol" liberating formaldehyde from its anhydromethylenecitrate component in alkaline media. A priori this proposition can be safely answered in the negative on the basis of the results, and deductions drawn therefrom, in the forepart of the paper. Nevertheless, some observations were made along this line.

Liberation of formaldehyde from anhydromethylenecitrate in ammoniacal urines. A portion of each urine of experiments 1 and 2 was allowed to stand at room temperature, and another portion was incubated at 38°C. for the development of ammonia.

This occurred in all specimens on the day following the administration of the drug, i.e., in about twenty hours. The urines were all precipitated and foul smelling. They were allowed to stand for several days and aerated into ammonia water and tested with phloroglucin as described previously for the liberation of free formaldehyde. The true reactions were obtained

TABLE 3

Liberation of formaldehyde from anhydromethylenecitrate in and reaction of ammoniacal urines

URINES OF EXPERIMENT 1				URINES OF EXPERIMENT 2			
Number of specimen	Ammoniacal and foul (+ = positive)	pH value end of 72 hours	Free formaldehyde by aeration (− = absent)	Number of specimen	Ammoniacal and foul (+ = positive)	pH value end of 72 hours	Free formaldehyde by aeration (− = absent)
At room temperature							
1	+		−	1	+		−
2	+	12.12	−	2	+	12.12	−
3	+	7.3	−	3	+	12.12	−
4	+	8.2	−	4	+	8.4	−
5	+	7.1	−	5	+	8.0	−
6	+	7.2	−	6	+	8.0	−
				7	+		−
Incubation at 38°C.							
1	+	12.0 (about)	−	1	+		−
2	+	12.12	−	2	+	12.12	−
3	+	8.0	−	3	+	12.12	−
4	+	<12.2	−	4	+	12.13	−
5	+		−	5	+	12.0 (about)	−
6	+		−	6	+		−
				7	+		−

colorimetrically by matching against standards of definite pH values in the usual way. The results are presented in table 3.

It is seen that the presence of free formaldehyde could not be demonstrated in even the most ammoniacal urine (pH 12.12). Bearing in mind that anhydromethylenecitric acid or the citrate, does not begin to liberate formaldehyde until the alkalinity corresponding to pH 13.07 is reached, it is obvious why formaldehyde could not be demonstrated in these urines. That is, none

was sufficiently alkaline, the highest alkalinity reached being the equivalent of pH 12.12. The urines standing at room temperature were even less alkaline as indicated by the pH values of 7.1 to 8.4. Therefore, no liberation would be expected in these, and no formaldehyde was found. The highest alkalinities observed (pH = 12.12) corresponded to the alkalinity of a solution of $\frac{N}{100}$ sodium hydroxide, or what is equally probable, that of normal $(\frac{N}{1})$ ammonium hydroxide whose pH value = 11.77. In urines such differences as occur between the values of pH = 12.12 and pH = 11.77 are practically negligible as it is not always easy to match the colors precisely because of the interference from color of urine itself. In these particular urines the turbidity also interfered somewhat and was difficult to remove by filtration. We may say, therefore, that the ammoniacal alkalinity of these decomposed urines corresponded closely to that of a normal $(\frac{N}{1})$ solution of ammonium hydroxide, or 1.7 per cent of ammonia.

It is reasonably certain that such a degree of alkalinity is never met with in life, and indeed would be practically intolerable to the bladder mucosa. Continuous excretion of urine would have the tendency to maintain the ammoniacal decomposition, therefore the alkalinity, at a lower level. Granted that the alkalinity necessary for the liberation of formaldehyde from anhydromethylenecitrate might be reached by ammonia, the liberated formaldehyde would be at once converted into hexamethyleneamine because of its great avidity for the ammonia. This principle is used for the quantitative estimation of formaldehyde or ammonia as the case may be. This would leave a compound not decomposable in alkaline media, bringing us back to the more rational method of therapeutic treatment, namely, rendering the urine acid first and then administering hexamethyleneamine in the usual way. Needless to say none of the urines containing anhydromethylenecitrate remained sterile, as indicated by the prompt ammoniacal decomposition, even those rendered previously alkaline (experiment 2).

From all this, it is to be concluded that, as a urinary antiseptic for acid, alkaline and ammoniacal urines, anhydromethylenecitric

acid is a complete failure. It has been adequately shown by the results of this study that formaldehyde liberation from this compound does not and can not occur under conditions of chemical reaction in the body. This is the chief reason for its failure as an antiseptic. Its antiseptic efficiency would be weakened further because it is almost entirely destroyed in its passage through the body.

"Citarin." This is the sodium salt of anhydromethylenecitric acid. Since the acid is neutralized by the bicarbonate of the intestine, what is absorbed into the circulation and excreted into urine is really the sodium salt. Therefore, what has been said throughout the text about anhydromethylenecitric acid as to destruction, liberation of formaldehyde and excretion applies to "citarin." Hence, its efficiency as a urinary antiseptic is to be regarded as negligible.

"Helmitol." This is said to be hexamethyleneamine anhydromethylenecitrate. The behavior of its anhydromethylenecitric acid component is strictly the same as that of the pure acid, except for some difference in acidity. Quantitatively, its relations would be about one-half those of the pure acid. The mechanism of action of hexamethyleneamine is well understood from work previously reported (10). This portion of "helmitol," of course, would act no differently from hexamethyleneamine. "Helmitol," therefore, represents nothing original over its components as a contribution to the field of urinary antisepsis. At any rate it can claim no special usefulness because of it anhydromethylenecitrate component.

SUMMARY

1. Anhydromethylenecitric acid is slowly soluble in water and acids and more readily in alkalies, which decompose it with the liberation of free formaldehyde.

2. The degree of alkalinity necessary for this is rather high as indicated by the hydrogen ion concentration, requiring a pH value of 13.06, corresponding to the alkalinity of a decinormal sodium hydroxide solution. High concentrations of bicarbonate

($\frac{N}{10}$, 1 and 2 per cent) do not liberate formaldehyde from anhydromethylenecitric acid.

3. Very high degrees of acidity (concentrated sulphuric acid) also decompose anhydromethylenecitric acid. On incubation, a lower acidity suffices, namely, pH = 0.1 and pH = 1.0.

4. Decomposition by hydrolysis with liberation of formaldehyde occurs in aqueous solutions on standing.

5. Moderate heating and distillation with alkali destroy about one-half of the anhydromethylenecitric acid.

6. The decomposition with formaldehyde liberation appears to be a reversible reaction.

7. Anhydromethylenecitric acid is excreted as the citrate in urine to the extent of only about 4.5 per cent, the remainder being probably destroyed in its passage through the body.

8. Free formaldehyde is not demonstrable in either acid, alkaline or highly ammoniacal urines containing anhydromethylenecitrate. This would be expected, since the alkalinity attained (pH 11.77 to 12.12) even in the most ammoniacal urines was not that required (pH 13.07) for the liberation of formaldehyde. It is doubted whether this degree of alkalinity is attainable during life.

9. The administration of anhydromethylenecitric acid does not confer antiseptic qualities on urines previously rendered alkaline by the administration of bicarbonate, and even on ammoniacal urines. All such urines decompose readily.

10. "Citarin," or sodium anhydromethylenecitrate, behaves precisely the same way as anhydromethylenecitric acid after administration, and neutralization by the bicarbonate of the alimentary tract. Its antiseptic qualities are to be regarded as negligible.

11. "Helmitol," or hexamethyleneamine anhydromethylenecitrate, can behave no differently than its components. Except for its action as a hexamethyleneamine compound, it is inert and negligible as an antiseptic.

12. The rational use of hexamethyleneamine as a urinary antiseptic still remains unsurpassed among this class of agents.

REFERENCES

(1) Impens: Monatschf. f. Urologie, 1903, viii, 257; Deutsch. Arch. f. Klin. Med., 1905, lxxxii, 409.
(2) May, Percy: Chemistry of Synthetic Drugs. 1911, p. 208, Longmans.
(3) Abderhalden: Biochemisches Handlexikon, 1908, i, 1181.
(4) Denigé: Merck's Reagenzien Verzeichnis. 1913, p. 81.
(5) Foa: Soc. biol., 1916, lviii, 867; ibid., 1906, lviii, 1000.
(6) McLendon, Shedlov and Karfan: J. Biol. Chem., 1918, xxxiv, 1.
(7) Henderson and Palmer: J. Biol. Chem., 1913, xiv, 81.
(8) Michaelis, L.: Wasserstoffionenkonzentration. 1914, Berlin.
(9) Hanzlik and Collins: J. Biol. Chem., 1916, xxv, 231.
(10) Hanzlik and Collins: Arch. Int. Med., 1913, xii, 578.

THE DIAGNOSIS OF CHANCROID AND THE EFFECT OF PROPHYLAXIS UPON ITS INCIDENCE IN THE AMERICAN EXPEDITIONARY FORCES

JOSEPH EARLE MOORE

Baltimore, Maryland

During the twelve months intervening between March, 1918, and March, 1919, the writer was consulting urologist to the District of Paris, and in charge of the venereal disease service of the only purely "skin and venereal disease" hospital in the American Expeditionary Forces. During that period there was afforded opportunity to see over 4000 new cases, among which were more than 800 venereal ulcers. The experience gained by the study of this large number[1] of sores forms the excuse for this paper.

In a selected ten months' period (April to February inclusive) 693 venereal ulcers were encountered. The original diagnosis (made on the basis of the clinical appearance of the sore and at least one dark-field examination) was chancroid in 379 instances, or 54.5 per cent, and primary syphilis in 314, or 45.5 per cent. In order to obviate, if possible, the serious consequences of the development of unrecognized syphilis, an effort was made to follow each chancroid for at least eight weeks, but owing to military exigencies this was possible in only 135 cases. The methods employed in coming to a final diagnosis are worth while

[1] Porter, H. W., Arch. of Dermatol. and Syphilol., N. S. I., 15, states that in fourteen years, 225 patients with chancre have been seen at the Barnard Free Skin and Cancer Hospital; and in three years, 106 chancres at the Washington University Dispensary.

Keidel, Albert (personal communication), states that in the five years existence of the Syphilis Clinic of the Johns Hopkins Hospital, there have been, among 5500 new cases, only about 600 venereal ulcers.

detailing briefly, mainly for the reason that in civilian practice, there is a sad lack of their application.

History. In chancroid the incubation period is short, as a rule never more than ten days, in syphilis usually two to eight weeks, though it may be longer. If accurate data covering this point were obtainable, it would be very helpful. In any circumstances, definite information is often lacking; and under army conditions of discipline many men attempted to evade court martial by denying exposure, while others admitted multiple exposures; so that statements as to the incubation period were usually unreliable. Thus of 115 cases still diagnosed as chancroid after following with Wassermanns, in 103 the incubation period was stated as less than ten days; in 12 more than ten days (in 2 cases, twenty-five days, and in one case five weeks). On the other hand, in 20 cases in which the diagnosis was changed to syphilis because of the later development of a positive Wassermann, exposure was denied in 2 cases, there was a history of multiple exposures in 3, and the incubation period in the others was given as 3 (2 cases), 4, 6, 7, 8, 9, 10 (2 cases), 13, 20 (2 cases), 24, 32 and 35 days (which in the last five instances should certainly have precluded a diagnosis of chancroid).

Clinical appearance. Unless a sore was clinically typical of chancre, little or no stress was laid on its clinical characteristics, since "mixed sores" (secondarily infected chancres, or chancre developing in the site of a chancroid) were only too common. Every sore was suspected of being syphilis until proved otherwise. Great stress was laid, as it should be in civilian clinics, on exhausting every means to rule out syphilis, since early in the primary stage is truly the golden moment for satisfactory antisyphilitic treatment.

Dark-field examination. It was an unalterable rule that dark-field examinations should be carried out on every sore for three successive days before the search for the treponeme was abandoned. When a sore had been treated by a careless medical officer with an antiseptic, usually calomel ointment (which happened as frequently in the army as it does in civil life, in spite of oft repeated advice), it was dressed for three days with

sterile salt solution before dark-fields were attempted. It cannot be too strongly emphasized that while the presence of the treponeme means syphilis, failure to find it on one examination means nothing. In the 135 cases under discussion, repeated dark-fields were negative in 134 instances; in the remaining case T. pallida were found on the sixth examination.

Smears and cultures for B. ducrey. While it has been conclusively demonstrated that this organism is the cause of chancroid, it is exceedingly hard to find. In 81 cases, clinically chancroid, in which smears were made, the Ducrey bacillus was demonstrated 20 times; in 61 cases smears were negative. Cultures on serum blood agar were made 55 times, and were positive only 5 times. Obviously, therefore, these methods of microscopic and cultural diagnosis are not to be relied upon.

Wassermann reactions. In the Paris clinic we adopted as an arbitrary rule the following: A Wassermann reaction when first seen, thereafter once a week for the first eight weeks, and at the middle and end of the third month. All 135 of our cases were followed for more than eight weeks, 97 of them for more than twelve weeks. Of the total the diagnosis was changed to syphilis because of the appearance of a positive Wassermann reaction in 19, or 14.8 per cent. The positive reaction appeared at the following intervals after the appearance of the sore: during the first month, 8; second month, 5; third month, 6. The shortest interval before the appearance of a positive Wassermann was two weeks, the longest eleven weeks.

Auto-inoculation. This method of diagnosis is highly lauded by the French. In our hands it proved of little value, for two reasons: (1) Because of the difficulty of controlling ambulatory patients, who frequently developed large spreading ulcers at the site of inoculation, which were very difficult to heal; and (2) because so-called positive reactions (pustule in twenty-four to forty-eight hours) can be obtained from secondarily infected syphilitic ulcers, in which the spirochaete can be demonstrated. If inoculation is practised, the patient should be in a hospital under rigid control, and at the first appearance of a "take" the inoculated site should be thoroughly cauterized with the actual cautery.

Comparison of Paris statistics with American Expeditionary Forces and other armies. The fact that 54.4 per cent of venereal ulcers were originally diagnosed as chancroid was sufficiently striking, as compared with the incidence of this disease in civil life, to prompt inquiry into possible reasons. Even if it be accepted that of the 379 chancroids, the diagnosis must later have been changed to syphilis in 14.8 per cent, thus making a total of 323 chancroids to 370 chancres, the high proportion of soft sores is manifest. In the American Expeditionary Forces at large, not including the Paris District, this fact was even more striking, especially when compared to the proportions in the British and French armies.

TABLE 1

	TOTAL VENEREAL ULCERS	CHANCROID	PER CENT CHANCROID	SYPHILIS	PER CENT SYPHILIS
French army in 1916*	18,900	5,860	30.0	13,230	70.0
British army in England up to April, 1917†	27,000	6,000	22.2	21,000	77.7
Paris clinic	693	379	54.5	314	45.5
American Expeditionary Force‡	3,480	2,628	75.5	652	24.5

* Thibierge, Syphilis et l'Armee. Masson & Cie., Paris, 1917.

† Osler, Lancet, 1917, cxcii, 787.

‡ Figures taken at random from American Expeditionary Force: Base Section No. 1 for month of November; Base Section No. 2 total to February 1, 1919; American Expeditionary Force totals for weeks ending December 25 to January 29, inclusive.

Two reasons for the wide discrepancy between the incidence of chancroid in our army and in those of our Allies suggest themselves: (1) differences in the methods of handling venereal disease; and (2) the influence of our prophylactic system.

Methods of handling venereal disease. As for the first point, it was the routine in the French and British armies to evacuate all cases of venereal disease to special base hospitals, staffed by experts in diagnosis and treatment. The American Expeditionary Forces practice, on the other hand, was to handle all venereal disease so far as possible within the organization; and even in cases requiring hospital care, the original diagnosis for purposes of statistical report was practically always made by the organi-

zation medical officer, who usually had no special experience in or laboratory facilities for the diagnosis and treatment of venereal disease. The inevitable result of this policy, which has obvious incalculable military advantages in time of war, is a high percentage of incorrect diagnoses. In this way can be partially explained the difference between the figures of 75.5 per cent chancroid for the American Expeditionary Forces and 20 to 30 per cent for the British and French. A large proportion of the American Expeditionary Forces chancroids were probably chancres, and many will undoubtedly develop later manifestations of syphilis.

In the Paris District, this point did not so much obtain. There was a centrally placed venereal disease clinic to which all medical officers in the district were instructed to send venereal ulcers for diagnosis, and these instructions were faithfully adhered to. Thus the 54.5 per cent chancroids represents diagnosis by a small group of men, all of whom had special training in venereal disease work, and in addition had at their disposal all the necessary laboratory facilities.

Influence of prophylaxis. The second factor which led to a higher percentage of chancroid in the American Expeditionary Forces as opposed to the lower figures in other armies was the almost universal use of prophylaxis. In no other army was routine prophylaxis a feature. Ashburn,[2] who was also struck by the frequency of chancroid, states as his impression that prophylaxis, as commonly used, was less effective against chancroid than against gonorrhea or syphilis. That the reason for this was in all probability due to the frequent omission of one of the important steps in the treatment will be shown in the following paragraphs.

Though it was commonly written of our prophylaxis that protargol prevents gonorrhea and that calomel ointment prevents syphilis and chancroid, we gradually came to feel certain that calomel ointment, however thoroughly applied, played little or no part in the prevention of chancroid. Attention was focused

[2] Ashburn, P. M., Factors making for a low venereal record in the American Expeditionary Forces. J. A. M. A., lxxiii, 1824, December 13, 1919.

on this point because of the following circumstance: Seven men belonging to the same organization, one of whom had been for some time under treatment for syphilis of five years' standing, went together to the same house of prostitution, and had relations with the same woman. On their return to camp, all took prophylaxis, at intervals from the exposure of three-quarters to three hours. On the fifth day after, all developed penile sores, which were typically chancroid, and which in six cases were later complicated by suppurating bubo. In reviewing the method of prophylaxis at the camp, the only discoverable fault was that no soap and water had been employed. This led to inquiry as regards the incidence of chancroid following prophylaxis as compared with venereal disease in general. It was found that in 1681 cases of venereal disease (including gonorrhea, chancroid, and syphilis), it was claimed that prophylaxis had been taken in only 720 instances, or 41.7 per cent; while, when the inquiry was limited to chancroid alone, 58.5 per cent claimed to have had prophylactic treatment. Investigation of individual cases frequently showed that the feature omitted from the treatment had been the preliminary use of soap and water. We therefore gradually came to the conclusion that so far as chancroid was concerned, the use of calomel ointment was of no value, that the only effective prophylaxis was soap and warm water thoroughly applied, and that this was effective if applied early even if the skin had been abraded and the Ducrey bacillus inoculated directly

A few experiments along these lines were tried in our clinic. Five men were selected with clinically typical chancroids, and from the sores, three inoculations were made on the left arm at about 2 inches distance from each other. The top inoculation was left as a control; the middle was treated at various intervals after inoculation ranging from ten minutes to two hours with calomel ointment well rubbed in for five minutes by the watch; and the lower with tincture of green soap and warm water at the same intervals, thoroughly used for five minutes. In all cases the control was positive, as was the inoculation treated with calomel ointment, while the lesion treated with soap and water was uniformly negative.

In many prophylactic stations in the American Expeditionary Forces soap and water was not used at all, or was used very carelessly, especially in stations of organizations in the field. On the other hand, calomel ointment was thoroughly applied in most instances. It is definitely felt that by virtue of this fact, many cases of syphilis were prevented, whereas chancroids developed as if no prophylaxis had been taken at all, thus materially altering the usual percentage incidence.

SUMMARY

1. Study of 693 venereal ulcers in my service in an American Expeditionary Forces clinic resulted in an original diagnosis of chancroid in 379, and of primary syphilis in 314.

2. The history of incubation, the clinical appearance of the sore and the presence of the organism of Ducrey are no more than suggestive in ruling out primary syphilis.

3. All venereal ulcers should be repeatedly examined (for at least three consecutive days) by dark-field illumination, and local application of antiseptics or the cautery should never be practised till these examinations have been made.

4. All patients with chancroid should be followed by frequently repeated Wassermann reactions for at least three months. Of 135 cases so followed, a positive Wassermann developed in 19 cases, or 14.8 per cent.

5. The difference in the incidence percentage of chancroid and chancre in the American Expeditionary Forces and that in other armies is in all probability due to the modifying influence of our system of prophylaxis. It is felt that the universal use of calomel ointment prevented the development of many cases of syphilis, but had little or no influence on chancroid; while the failure to use, or carelessness in using, soap and water allowed chancroids to develop unhindered.

6. Experimental proof is presented to support this theory. In five cases, the application of green soap and warm water prevented the development of auto-inoculated chancroid, while calomel ointment had no such effect.

CONCLUSIONS

1. In attempting the diagnosis of venereal ulcers, in civil as well as military practice, every effort should be made, by the use of dark-field examinations and repeated Wassermanns, to rule out syphilis before arriving at a definite diagnosis of chancroid.

2. If prophylaxis against venereal disease is carried out, it should include as one of its cardinal steps, in order that chancroid be prevented, the liberal use of soap (preferably green soap) and warm water.

THE ANTISEPTIC PROPERTIES OF NORMAL DOG URINE AS INFLUENCED BY DIET

R. F. HAIN

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital

In a previous article by Davis and the author (1), attention is called to the fact that normal, drug-free dog urine is sometimes bactericidal for the colon bacillus but has no such action on the Staphylococcus albus. The study of normal dog urine was continued in the hope either of isolating some substance responsible for this germicidal action toward the colon bacillus, or of determining whether this property is due to some physical alteration which can be duplicated in human urine. The preliminary problem presenting itself was to determine whether it is possible to control the germicidal action of dog urine toward the colon bacillus, and the results of the experiments carried out with this end in view are given in this paper.

Variations in the diet which might explain the presence of some compound in the urine at irregular intervals or in the fluid intake which would bring about alterations in the concentration of the urine were first considered as factors possibly responsible for the inconstancy of this bactericidal property.

Male dogs, as they came to the laboratory, regardless of breed, were used for the study. The only requirements were that the dog's urine be sterile, and that they be easy to catheterize, this being an important factor in collecting sterile specimens. Fifteen dogs were used during the experiments, but only 8 could be used throughout, 6 being rejected because of difficulties attending catheterization, and 1 because of an infection occurring at the beginning of the study. The specimens were collected each morning before feeding so that the time element in regard to food intake was constant. The catheterizations were done with aseptic precautions, the glans penis and the anterior urethra

being carefully irrigated with a 1-10,000 bichloride of mercury solution before each catheterization. With this technique 94 per cent of the specimens collected from uninfected dogs were sterile.

B. coli and S. albus were used for inoculating the specimens. B. coli was employed because it is the most frequent invader of the genito-urinary tract of man, and because it grows well in urine

TABLE 1

Dogs fed unknown amounts of ground beef and given water ad lib.

DATE	DOG 1			DOG 2			DOG 3			DOG 5			DOG 7			DOG 10			DOG 11		
	−	α	∂	−	α	∂	−	α	∂	−	α	∂	−	α	∂	−	α	∂	−	α	∂
3- 7-19	0	25	∞	0	15	∞	0	0	∞												
3- 8-19	0	∞	∞	0	5	∞	0	0	∞												
3- 9-19	0	0	∞	0	∞	∞	0	∞	∞												
3-10-19	0	100	∞	0	0	∞	0	0	0												
3-11-19	0	∞	∞	0	50	∞															
3-12-19	0	50	∞	0	0	∞	50	50	50	0	0	∞									
3-13-19	0	0	∞	0	0	∞	0	0	0	0	0	∞	0	∞	∞						
3-14-19	0	300	∞	0	100	∞	0	0	0	0	0	∞	0	∞	∞						
3-15-19	0	∞	∞	0	∞	∞	0	0	0	0	0	∞	0	0	∞						
3-16-19	0	∞	∞	0	∞	∞	0	0	25	0	0	∞	0	∞	∞						
3-17-19	0	∞	∞	0	0	∞	0	0	0	0	0	∞	0	0	∞						
3-18-19	0	100	∞	0	0	∞	0	0	0	0	0	∞				0	0	∞			
3-19-19				0	200	∞				0	0	∞	0	0	∞	0	25	∞			
3-20-19	0	100	∞	0	100	∞	0	0	0	0	0	∞	0	0	∞	0	0	∞			
3-21-19	0	∞	∞	0	0	∞	0	0	100	0	0	∞	0	0	∞	0	50	∞			
3-22-19	0	0	∞	0	0	∞				0	0	∞	0	0	∞	0	100	∞	0	0	∞
3-23-19	0	0	∞	0	0	∞	0	0	0	0	0	∞	0	0	∞	0	200	∞	0	0	∞
3-24-19	0	20	∞	0	0	∞				300	300	∞	0	0	∞	0	0	∞	0	0	∞
3-25-19	0	∞	∞	∞	∞	∞	0	0	0	0	0	∞	0	0	∞	0	50	∞	0	0	1000

− = Control plates; α = B. coli; ∂ = S. albus; 0 = no growth after twenty-four hours incubation; ∞ = profuse growth in twenty-four hours.

as a culture medium. S. albus was used because it is a common invader of the genito-urinary tract of man, because it is more resistant in dogs' urine as a culture medium than S. aureus (1), and because it has frequently been used for similar experiments.

The specimens of urine were inoculated with B. coli and S. albus as follows: From every specimen collected three 5 cc. portions were transferred to sterile test tubes. One of the tubes was

then inoculated with a loop of a twenty-four hour broth culture of B. coli, another with a loop of a twenty-four hour broth culture of S. albus, and the third tube was used for a control. The tubes with their contents were then incubated for twenty-four hours, after which 0.1 cc. was transferred to a melted agar tube and a plate poured, the plates being incubated for twenty-four hours. If the control plate was sterile, it was assumed that the negative or positive findings on the other plates indicated the presence or absence of the bactericidal property.

At the beginning of this study the dogs were fed approximately ½ pound of ground beef daily, regardless of size or weight, and allowed water ad lib. Seven dogs were fed on this diet for a period of nineteen days, during which time 90 specimens were collected. Three and three-tenths per cent of these specimens were contaminated, 10 per cent killed B. coli and S. albus, and 60 per cent killed B. coli but not S. albus (see table 1).

After confirmation of the findings just noted the dogs were weighed weekly, and their food intake calculated accurately per kilogram of body weight. The observation that foods high in protein probably increased the percentage of bactericidal specimens was made at this time.

OBSERVATIONS

1. From April 22 to May 5 six dogs were fed 40 grams of liver per kilogram of body weight and allowed water ad lib. During this interval 71 specimens were collected, of which 8.4 per cent were infected; and 80.3 per cent contained the germicidal property for B. coli; and 18.3 per cent made an unfavorable culture medium for both B. coli and S. albus.

2. Eight dogs were fed 50 grams of liver per unit of body weight, allowed water ad lib and catheterized daily from May 7 to May 13. During this interval 52 specimens were collected and all were sterile. S. albus and B. coli were killed in 3.8 per cent of the specimens collected, while 80.7 per cent killed B. coli but not S. albus (see table 2).

3. The dogs were fed 50 grams of spleen per kilogram of body weight, and allowed water ad lib for six days. During this in-

terval 47 specimens were collected, all being sterile, of which 6.3 per cent killed both organisms under observation, and 72.3 per cent killed the B. coli but not S. albus.

4. The influence of the concentration of the urine upon these results was considered at this time. The dogs were given 50 grams of liver per kilogram of body weight as before and in addition the quantity of water allowed was carefully measured. While on the same amount of liver the dogs were divided into two

TABLE 2

Table showing results of feeding 50 grams liver per kilogram of body weight daily and water ad lib.

DATE	DOG 1			DOG 2			DOG 3			DOG 5			DOG 7			DOG 10			DOG 12			DOG 15		
	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂			
5- 7-19	0	∞	∞	0	100	∞	0	0	25	0	0	∞	0	0	∞	0	25	∞	0	0	∞			
5- 8-19	0	0	∞	0	1000	∞	0	0	50	0	0	∞	0	0	0	0	0	∞	0	0	100	0	0	∞
5- 9-19	0	0	∞	0	0	∞	0	0	50	0	0	∞	0	0	∞	0	0	∞	0	0	25			
5-10-19	0	0	∞	0	200	∞	0	0	0	0	200	∞	0	0	∞	0	0	∞	0	∞	∞	0	0	∞
5-11-19	0	0	∞	0	0	∞	0	0	∞	0	0	75	0	0	∞	0	0	∞				0	0	∞
5-12-19	0	0	∞	0	500	∞	0	0	∞	0	0	200	0	0	∞	0	50	∞	0	0	200	0	200	∞
5-13-19	0	0	∞	0	0	∞	0	0	∞	0	0	500	0	0	∞	0	0	∞				0	0	∞

– = Control plates; α = B. coli; ∂ = S. albus; 0 = no growth after twenty-four hours incubation; ∞ = profuse growth in twenty-four hours.

groups of four each, one group being given 10 cc. of water daily per kilogram of body weight. The other group received each 40 cc. by stomach tube twice daily, besides being allowed to drink at will. On this routine 40 specimens were collected from the dogs receiving the large amount of water; of these 17.5 per cent were contaminated. None of these specimens proved to be an unfavorable culture medium for the S. albus, and only 20 per cent possessed germicidal properties for B. coli. Thirty-seven specimens collected from the group receiving only 10 cc. of water per kilogram of body weight per day were all sterile; 97 per cent were germicidal for B. coli and 32.4 per cent were germicidal for S. albus as well (see table 3).

These results seemed to show that the concentration of the urine was an important factor. Therefore, the dogs were put

on 75 grams of liver and 10 cc. of water per kilogram of body weight per day. Two days were allowed without collecting of specimens between the change from 50 to 75 grams of liver per kilogram, in order that the new conditions might become sta-

TABLE 3

Table showing results from feeding 50 grams liver per kilogram body weight

DATE	WATER AD LIB. + 80 CUBIC CENTIMETERS PER KILOGRAM THROUGH STOMACH TUBE												ALLOWED 10 CUBIC CENTIMETERS OF WATER PER KILOGRAM											
	Dog 1			Dog 2			Dog 12			Dog 15			Dog 3			Dog 5			Dog 7			Dog 10		
	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂
5–20–19	0	∞	∞	0	0	∞	0	∞	∞	0	0	∞	0	0	0	0	0	0	0	0	∞	0	0	∞
5–21–19	0	∞	∞	0	0	∞	0	0	∞	∞	∞	∞	0	0	0	0	0	100	0	0	∞	0	0	0
5–22–19	0	∞	∞	0	∞	∞	∞	∞	∞	0	∞	∞	0	0	0	0	0	1000	0	0	∞	0	0	∞
5–23–19	0	∞	∞	0	0	∞	∞	∞	∞	0	1000	∞	0	0	0	0	0	0	0	0	∞	0	0	∞
5–24–19	0	∞	∞	0	∞	∞	0	100	∞	∞	∞	∞	0	0	0	0	0	∞	0	0	∞	0	∞	∞
5–25–19	0	∞	∞	0	0	∞	∞	∞	∞	0	0	∞	0	0	0	0	0	0	0	0	∞	0	0	∞
5–26–19	0	∞	∞	0	200	∞	∞	∞	∞	0	∞	∞	0	0	0	0	0	∞	0	0	∞	0	0	∞
5–27–19	0	∞	∞	0	∞	∞	∞	∞	∞	0	∞	∞	0	0	0	0	0	∞	0	0	∞	0	0	∞
5–28–19	0	∞	∞	0	200	500	0	0	∞	0	∞	∞				0	0	200	0	0	∞	0	0	∞
5–29–19	0	∞	∞	0	200	∞	0	∞	∞	0	∞	∞							0	0	∞	0	0	∞

– = Control plates; α = B. coli; ∂ = S. albus; 0 = no growth after twenty-four hours incubation; ∞ = profuse growth in twenty-four hours.

TABLE 4

75 grams of liver and 10 cc. of water per kilo each day

DATE	DOG 1			DOG 2			DOG 5			DOG 7			DOG 10			DOG 12			DOG 15		
	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂
5–31–19	0	0	∞	0	0	0	0	0	0	0	0	∞	0	0	∞	0	0	∞	0	0	∞
6– 1–19	0	0	∞	0	0	0	0	0	0	0	0	∞	0	0	∞	0	0	∞	0	0	0
6– 2–19	0	0	∞	0	0	200	0	0	1000	0	0	200	0	0	∞	0	0	200	0	0	∞
6– 3–19	0	0	∞	0	0	100	0	0	200	0	0	300	0	0	∞	0	0	∞	0	0	∞
6– 4–19	0	0	∞	0	0	∞	0	0	∞	0	0	∞	0	0	∞	0	0	∞	0	0	∞

bilized. The dogs were catheterized for five days and 35 specimens were collected without any contaminations. One hundred per cent of the specimens were germicidal for B. coli and 14 per cent were germicidal for S. albus in addition. From this time on part of the food was refused, and this series was discontinued (see table 4).

A diet high in protein and low in water having produced constantly germicidal urines, studies on a diet low in protein were made. For this purpose 15 grams of white bread and 25 cc. of fresh milk per kilogram of body weight per day, with water ad lib, were allowed. The dogs were not catheterized for two days after they were put on the bread and milk diet. From June 6 to June 13 inclusive 56 specimens were collected, none of which had any germicidal action toward the organisms under cultivation, while 14.3 per cent were contaminated (see table 5).

TABLE 5

Dogs fed 15 grams white bread and 25 cc. of fresh milk daily plus water ad lib.

DATE	DOG 1			DOG 2			DOG 5			DOG 7			DOG 10			DOG 12			DOG 15		
	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂	–	α	∂
6- 6-19	∞	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6- 7-19	∞	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6- 8-19	∞	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6- 9-19	∞	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6-10-19	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6-11-19	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞
6-12-19	∞	∞	∞	0	∞	∞	0	∞	∞	∞	∞	∞	0	∞	∞	0	∞	∞	∞	∞	∞
6-13-19	0	∞	∞	0	∞	∞	0	∞	∞	0	∞	∞	∞	∞	∞	0	∞	∞	0	∞	∞

– = Control plates; α = B. coli; ∂ = S. albus; 0 = no growth after twenty-four hours incubation; ∞ = profuse growth in twenty-four hours.

One hundred and twenty-nine specimens were collected while the dogs were being fed 50 grams of liver per kilogram of body weight per day of which 4.6 per cent were contaminated, 66.5 per cent killed B. coli, and 10.9 per cent killed both organisms studied. The germicidal action of dogs' urine toward B. coli when the dogs are fed 50 grams of liver per kilogram of body weight per day is inversely proportional to the quantity of water ingested. While on this diet the dogs receiving 10 cc. of water per kilogram of body weight per day excreted urine of which 97 of the specimens displayed germicidal properties toward B. coli. When the dogs were allowed water ad lib 80.3 per cent of the specimens killed B. coli, while only 20 per cent of the specimens recovered, while 80 cc. of water was being administered by stomach tube daily were fatal to this organism.

In all 428 specimens are tabulated of which 13 per cent were collected from dogs fed on bread and milk, 5.6 per cent of all the specimens collected were contaminated, and 33.3 per cent of all the contaminated specimens were collected from dogs fed on bread and milk, 62.3 per cent of all the specimens killed B. coli, 10 per cent killed both B. coli and S. albus, but S. albus was not killed in any specimen which did not also kill B. coli.

While studying the antiseptic properties of some mercury compounds, using human urine as a culture medium, it was noted that S. albus was always killed by much more dilute solutions than B. coli. With this antiseptic dog urine, on the other hand, B. coli was more readily killed than S. albus. It appears, therefore, that the substance responsible for this phenomenon in dog urine has a selective action for B. coli.

During the interval from March 25 to April 21, 1919, dogs 12 and 13 were fed on approximately ½ pound of ground beef every second day, and allowed water ad lib, for two weeks. While on this diet their bladders quickly became infected, a condition which lasted from April 8 to April 24 in dog 12, and from April 15 to May 31 in dog 13. The organism isolated from a specimen of urine taken from dog 13 was S. albus, but that responsible for the infection of dog 12 was not determined. The urines of both of these dogs were free of infection on the last date mentioned above responding like that of the other dogs to changes in diet by becoming more germicidal for B. coli. Dog 12 was again put in the group for study, but dog 13 was not included.

CONCLUSIONS

1. The antiseptic property of normal, drug-free dog urine toward B. coli can be controlled by regulating the diet and the quantity of water ingested.

2. If a definite quantity of liver per kilogram of body weight per day representing a food high in protein be fed, the bactericidal property of dog urine is inversely proportional to the quantity of water ingested.

3. If a constant quantity of water be given daily, the germicidal property of dog urine toward B. coli varies distinctly with the quantity of animal food high in protein, as liver, ingested.

4. The urine of dogs fed on bread and milk is not germicidal toward B. coli or S. albus.

5. Dog urine has a selective germicidal action on B. coli when the animals are fed on animal food high in protein, since many specimens from these dogs are fatal to B. coli but innocuous to S. albus.

6. The specimens collected from dogs fed on meat are not so easily contaminated as those collected from dogs fed on bread and milk.

REFERENCES

(1) Davis, Edwin G., and Hain, R. F.: Urinary antiseptics: The antiseptic properties of normal dog urine. Jour. Urol., ii, August 4, 1918.

(2) Hawk, Philip B.: Practical Physiological Chemistry, 1916, p. 559.

OBSERVATIONS ON GUN-SHOT WOUNDS OF THE URETHRA

J. A. C. COLSTON

From the James Buchanan Brady Urological Institute The Johns Hopkins Hospital Baltimore, Maryland

The relative rarity of injuries to the genito-urinary tract noted in a general military hospital has already been commented upon by numerous observers. Wounds of the bladder are usually associated with injuries to other viscera and a large proportion of these cases do not survive long enough to reach an evacuation or base hospital. Wounds of the urethra, too, are invariably associated with injuries to adjacent structures and the immediate mortality depends largely on the extent of these complicating wounds. Following an injury to the urethra there is usually obstruction to urination and often a rapid extravasation of urine. On this account these cases urgently require immediate attention but, unfortunately, conditions on the field are such that it is rare for the wounded man to receive surgical intervention within six hours from the time of the infliction of his wound. The poor prognosis which most writers have noted in this type of case is dependent on this unavoidable delay, during which time the surrounding tissues, devitalized by the trauma of the projectile and the increasing extravasation of urine, form a most favorable medium for the growth of microörganisms carried into the wound by the projectile. Stevens was impressed by the small number of cases of genito-urinary wounds seen in base hospitals and by their high mortality. French statistics show a mortality of 56 per cent for non-complicated bladder wounds and of fifteen cases in which both the bladder and intestines were injured, only one patient survived. Stevens observed four patients with perineal wounds, only one of whom recovered.

Certain cases which were observed in a base hospital in France and which illustrate the principle which should be followed in their treatment will be reported. The first case is particularly interesting in that it brings out the numerous complications which may follow a gun-shot injury of the genito-urinary tract and emphasizes the importance of the after care of these difficult cases.

Case 1. P. H. G., private, 23d Infantry, was wounded on June 14, at 2.00 p.m., by a shell fragment which entered the posterior aspect of the right thigh, passed just posterior to the femur, the exit wound being on the inner aspect of the thigh close to the perineum. The projectile then entered the perineum, severed the urethra close to the bulb, divided the left spermatic cord, and tore its way out through the abdominal wall in the left inguinal region without entering the peritoneal cavity. The patient arrived at a mobile hospital at 10.00 p.m., where antitetanic serum was administered and immediate operation performed. The operation consisted of debridement of the thigh wound, left castration and suprapubic cystostomy. The patient's field card contained the following brief notes made at the mobile hospital:

June 18. Thigh wound dirty and discharging large amount of foul pus.

June 19. Suprapubic incision infected. Dorsal surface of penis swollen with definite crepitation—culture showed gas bacilli, Suprapubic incision opened, necrotic tissue excised; four incisions made on the dorsal surface of the penis and Dakin's tubes placed in all wounds, a large tube left in bladder. Thigh wound discharging fecal material (this fact was not corroborated at the later examination of the patient after evacuation. The copious foul discharge of an extensive, badly infected wound especially in this region may well lead one to suspect an injury of the bowel).

Patient evacuated June 22.

On arrival at Base Hospital 18 on June 23, the patient's general condition was poor. Examination revealed a large sloughing wound of the hypogastric region measuring about 3 by 4 inches. The slough involved the fascia and recti muscles. A large tube was in the bladder and the wound was bathed in very foul urine. The debrided thigh wound was discharging large amounts of foul pus. An incision in the left groin and upper portion of the scrotum had broken down, and four incisions on the dorsal surface of the penis were also obviously infected, but no

crepitation could be demonstrated in the surrounding tissues. All wounds were treated with continuous Dakin's solution and frequent dressings done. The wounds became slowly cleaner and the general condition of the patient somewhat more favorable until June 28, fourteen days after the patient was wounded. On this date clonic spasms associated with severe pain in the region of the thigh wound were noted. On the following day the spasms were more severe, a slight trismus was present, and the reflexes were hyperactive. A diagnosis of tetanus was made, and 20,000 units of antitetanic serum was administered. The general condition was worse the next day and a lumbar puncture withdrew fluid under tension. During the next few days the general condition remained unchanged, and morphia, sodium bromide and chloral hydrate were used to combat the spasms and opisthotonos, which had now appeared. The patient received 10,000 units of antitetanic serum subcutaneously each day. On July 3 a second lumbar puncture was done and 20,000 of antitetanic serum given intraspinally.

Steady improvement in the general condition now began. On July 6, the patient had so improved that an external urethrotomy was done under ether anaesthesia. From this date the wounds became rapidly cleaner and the patient stronger, and, although definite trismus was still present, together with occasional spasms, the antitetanic serum was no longer given. The suprapubic tube was now removed and the good effect of the dependent drainage afforded by the external urethrotomy was soon demonstrated in the condition of all the wounds. Several large sloughs separated from the suprapubic wound and the thigh wound filled in rapidly. Two large bedsores, which had developed during the course of the tetanic infection, also began to share in the general improvement. On August 1 a slight stiffness of the jaw persisted, but the spasms had not been noted for some days. This trismus, the last sign of tetanus, disappeared in the next few days. During this time, the urethra, anterior to the point at which it had been severed, was kept patent by means of a permanent catheter and by the frequent passage of sounds. On August 16, the patient was voiding through the perineal fistula with perfect control. The anterior urethra was patent from the meatus to the perineum in close proximity to the urethrotomy wound. The suprapubic wound had healed firmly and the thigh wounds and bedsores were closed except for healthy granulating areas. It was hoped at a later operation to restore the continuity of the urethra by a plastic operation. However, owing to the fact that the hospital was at this time functioning as an evacuation hospital, it was necessary to evacuate the patient on account of the exigencies of the service.

The patient was again seen in June, 1919. His general condition was excellent, all wounds were healed and he had perfect control of the urine, which passed entirely by the perineal fistula. The urethra anterior to the fistula had been allowed to close and was entirely obliterated. The patient is to return at a later date for a plastic reconstruction of the canal.

Better drainage could have been obtained in this case, and it is probable that some of the sloughing of the abdominal wall would have been avoided had an external urethrotomy been done at the same time as the cystostomy. The latter operation alone will not entirely prevent some urine from extravasating into the injured tissues about the urethra, and this factor was undoubtedly responsible for part, at least, of the very foul infection of the patient's thigh wound. The complication of tetanus, in spite of the prompt administration of antitetanic serum at the field hospital, illustrates the wisdom of the orders of the Chief Surgeon, A. E. F., that a second prophylactic injection should be given in all seriously wounded men, within two weeks after the first injection. Finally the fact that the patient ever recovered in spite of so many and such grave complications is due entirely to the constant and devoted attention he received from the nursing staff of the hospital.

Plans had at this time already been drawn up for a special hospital for urological cases alone, and had it been possible to evacuate this man to such a hospital, where he would have had the benefit of the attention of skilled urologists, much might have been done to prevent the unfortunate ultimate result. Reconstruction of the anterior urethra in this case, after the lapse of such a long time, will be a very difficult procedure, one which will require several operations and ultimate success is by no means assured.

Case 2. W. B., Sergeant 30th Infantry, was wounded by a rifle bullet on June 20, 1918, the projectile entering the right side of the scrotum, severing the urethra at the peno-scrotal junction, entering the inner aspect of the left thigh and making its exit by the gluteal fold of the left thigh.

The patient was admitted to Field Hospital 27 where "paralysis of left leg, no injury to femur" was noted. A catheter could not be passed. A suprapubic cystostomy was done and the patient was evacuated. At Evacuation Hospital 7 it was found "impossible to catheterize either anterior or retrograde."

The patient was admitted to Base Hospital 18 on June 23, in poor condition. Under ether, the thigh wounds were opened and a large accumulation of pus evacuated. This pus cavity surrounded the sciatic nerve, but the nerve itself was apparently uninjured. It was again impossible to pass a catheter either by the meatus or in retrograde fashion through the suprapubic wound. The thigh wounds were treated by Dakin's solution and the general condition of the patient rapidly improved. The suprapubic wound drained well, the incision was clean and the bladder was apparently not badly infected.

On July 8, under ether, an external urethrotomy was performed, and an attempt made to approximate the torn ends of the urethra. A tube was placed in the bladder through the perineal wound and the suprapubic tube removed. On July 13, a catheter was passed by way of the meatus out into the perineal wound where it was reintroduced into the bladder. The perineal wound was now closed over this continuous catheter with a small protective drain to take care of any leakage. The suprapubic wound closed a few days later and on July 20, the catheter was withdrawn. The patient was able to void naturally, but within forty-eight hours urine was leaking both by the suprapubic and by the perineal wounds. The catheter was reintroduced from meatus to bladder and the suprapubic wound promptly healed. The catheter was withdrawn in seven days, and gradual dilatations of the urethra commenced. On August 10, it was necessary to evacuate the patient. He was now in excellent condition, the thigh wounds closed except for small granulating areas. The sensory and motor paralysis of the sciatic nerve showed distinct improvement and, as the continuity of the nerve had been demonstrated at operation, it was considered probable that complete function would be restored. The patient was voiding at normal intervals clear, uninfected urine, and a number 24 sound could be introduced into the bladder. A small perineal fistula was present through which a few drops of urine leaked.

This case was a very satisfactory one in every particular, and, in spite of the fact that an external urethrotomy was not done until some time had elapsed, the cystostomy took care of the

urine and there was little or no infection in the suprapubic wound or in the bladder itself. This good result is in part, at least, due to the fact that the wound was caused by a rifle bullet. In general, it may be stated that wounds from shell fragments are more lacerated, cause more damage to surrounding tissues and are far more liable to be followed by severe infection.

Case 3. E. G., private 39th Infantry, was wounded by machine gun bullets on August 5. One bullet passed through the soft part of the left leg and a second entered the upper and inner portion of the right thigh, passed into the perineum, severed the membranous urethra with fracture of the ischium and extravasation of urine. At Field Hospital 19, the wounds of the soft parts were debrided, an external urethrotomy with plastic reconstruction of the urethra and a suprapubic cystostomy were done.

The patient was admitted to Base Hospital 18 on August 9 in good condition. The bladder was draining well by suprapubic and perineal tubes, the debrided wounds of the soft parts were clean, but the suture line of the incision in the perineum was badly infected. Three stitches were removed, a large amount of foul pus evacuated and all wounds were treated by continuous Dakin's solution.

On August 14 all wounds were cleaner. The suprapubic tube was removed and all urine was passing by the perineal tube. It was possible to pass a catheter through the meatus into the perineal wound and it was planned to treat this case by the method which had been used in case 2. However, at this time a general evacuation of the hospital was ordered to prepare for fresh convoys of casualties and it was unfortunately necessary to evacuate the patient.

This case illustrates the inadvisability of attempting any plastic procedures for the repair of the urethra at the first operation. It was necessary to open the perineal wound widely, introduce Dakin's tubes and undoubtedly the resulting scar will seriously hamper any further operative procedure for the repair of the urethra.

The medical authorities of the French army soon recognized the importance of special attention for urological cases and special urological hospitals were established in various regions to care for these patients. On account of this policy, French urologists

have had an unequalled opportunity to observe this type of case and they have made many contributions to the literature of the subject. Escat states that if the patient survives to reach a base hospital, the general immediate results are good, but that the end results are often disappointing. He emphasizes the long post operative attention to complications that is necessary, and remarks that the problem of a urethral wound is divided in two stages; first—efforts to combat retention and infection by means of suprapubic and wide urethroperineal incisions; and second—reparation by urethrorrhaphy or autoplastic procedures with continued deviation of the urine. For the repair of the urethra, Marion advises resection of the scar tissue interposed between the ends of the canal which is reconstructed by end to end suture. If the latter procedure is impossible, the periurethral tissues should be approximated over a catheter, and he emphasizes that a cystostomy must be maintained until recovery.

Le Fur cites a case illustrating the numerous complications which may result from a urethral wound in which eleven successive operations were performed, including resection of the hip and arthrotomy of the knee.

Pasteau performs a cystostomy and thoroughly opens the perineal wound. The torn ends of the urethra are placed in alignment and a permanent catheter inserted. Later on, he opens the perineal wound widely and explores any fistulous tracts, leaving them open for a long time, the cystostomy opening being maintained. He considers this the best procedure to prevent or to treat strictures.

Loumeau has cited an unusual case of urethral wound in which the patient was able to urinate after the injury. However, increasing difficulty finally necessitated external urethrotomy.

At a symposium on this subject, Legueu, Cathelin, Jeanbrau and other well known urologists reported their experience at the urological hospitals, and their conclusions in regard to the treatment of these cases may be summed up under three heads.

1. Deviation of urine by suprapubic cystostomy associated with a wide opening of the traumatized area.

2. Immediate suture, always a long and delicate operation, should only be attempted when associated with suprapubic deviation.

3. Evacuation of patients to urological hospitals and application of the procedure that seems best suited to the individual case for the repair of the urethral defect.

It is evident that the most urgent necessity in the case of a patient with a ruptured urethra from a gun shot wound is deviation of the stream of urine from the injured area and suprapubic cystostomy should immediately be done. At the same time external urethrotomy should be done, the tract of the projectile cleaned and some attempt made at approximating the ruptured ends of the canal. However, it would be rarely advisable to attempt a plastic repair, as sutures must almost invariably become infected. External urethrotomy alone should be done only in exceptional cases for, although this operation is amply sufficient in cases of ruptured urethra seen in civil practice, gunshot wounds offer a different problem on account of the danger of serious infection, and adequate drainage must be obtained on account of the long journey to which these patients must necessarily be subjected to reach a base hospital in time of war.

There is no type of case which requires more painstaking and tedious after care, and the best results can only be obtained in a special hospital under the direction of men who have had special training in urological surgery.

REFERENCES

Stevens: Experiences in France with surgery of genito-urinary tract. J. A. M. A., 1919, xxii, 1589.

Escat: Traitement des plaies de la vessie et de l'urètre, Jour. d'Urol., 1918, vii, 161.

Marion: Conduite à tenir dans les traumatismes de l'urètre postèrieur envisagés dans la zone de l'arrière. Jour. d'Urol., 1918, vii, 385.

Legueu, Cathelin, Jeanbrau and others: Traitement d'urgence des plaies de la vessie et de l'urètre; traitement des plaies du rein et de l'urètre dans la zone des armées et à l'arrière. Reported in Presse Méd., 1917, p. 706.

Chalier and Glenard: Plaies des organes génito-urinaires. Rev. de Chir., 1917, iii, 552.

Le Fur: Blessure par balle de la fesse et du bassin avec rupture étendue de l'urètre. Paris Chirurg., 1918, x, 313.

Cathelin: Procédés autoplastiques applicables au traitement des fistules de l'urètre, suites de blessures de guerre. Jour. d'Urol., 1918, vii, 267.

Le Fur: Refection par autoplastic d'une voluminuese perte de substance urètrale et d'une plaie étendue de la verge avec destruction partielle du gland. Paris Chirurg., 1917, x, 358.

Pasteau: Les lésions traumatiques de l'urètre profond. Jour. d'Urol., 1918, vii, p. 407.

Luys: War wounds of the genito-urinary organs. Med. Record, 1919, xcv, 734.

EPITHELIAL HYPERPLASIA IN CONGENITAL CYSTIC KIDNEYS

C. A. McKINLAY

From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine, New Haven, Connecticut

INTRODUCTION

Congenital cystic kidneys, so abundantly considered in the literature of the past few decades, present problems which are unusually interesting and difficult of interpretation. The prevailing view concerning their etiology is that they are the result of malformation, though many consider them new-growths—adenocystomata. Few have entertained the idea that proliferation of the epithelial lining of the tubules, even attempts to form new, possibly atypical, tubules, may be evidence of compensatory effort by the healthy parenchyma of an organ whose efficiency has been handicapped by malformation. However, this is the conclusion reached in the study of the case presented below.

CASE REPORT

F. F., hospital no. 65049, a white male aged thirty years, was admitted to the New Haven Hospital on January 2, 1918, complaining of "stroke."

The family and past histories are recorded as negative.

The present illness began two months before admission, when the patient became paralyzed on the left side. He recovered partially, and on January 24, a second "stroke" paralyzed the entire left side of the body.

Physical examination. The patient is semi-conscious and responds feebly to stimuli. The head is turned to the left. There is nystagmus. The pupils react slightly to light. Examination of the chest is negative. The blood pressure measures 230/130 mm. of mercury. The heart sounds are normal.

There is spasticity of the right arm and leg. The deep reflexes are exaggerated. Marked positive Babinski reflex and ankle clonus are present on the right. At times there are convulsive movements on the left side.

Lumbar puncture reveals a blood stained fluid under increased tension. The specific gravity of the urine is 1.018, and there is a slight trace of albumin with numerous granular casts. The white blood cells, 14,000 on January 25, increased to 31,000 by the next day. The Wassermann for the spinal fluid is 3 plus, but it is not recorded for the blood.

Anatomical diagnosis

Primary. (A) *Congenital cystic kidney:* Cardiac hypertrophy; arteriosclerosis; cerebral hemorrhage with extension into the cerebral ventricles.

Subsidiary. Syphilitic mesaortitis (1); purulent bronchitis; bronchopneumonia; infected pulmonary infarct; apical pulmonary scar; fibrous pleurisy; calcification of bronchial lymph glands; fibrosis of the appendix; fibrous peritonitis.

Protocol autopsy no. 30

The protocol is abstracted to include only those portions deemed essential for this presentation.

Kidneys. The right kidney measures 17 by 10 by 6 cm. Its surface presents numerous rounded elevations which vary from a few millimeters to 3 cm. in diameter. They all fluctuate, and those immediately beneath the surface have thin, transparent walls and contain straw colored fluid. On section the kidney is honeycombed with cysts varying from 3 mm. to 3 cm. in diameter. The cysts are, for the most part, smooth walled. In some places they appear multilocular. Some cysts contain fluid, straw colored or turbid and brownish-black, and others, a jelly-like mass. Between the cysts are irregular masses of kidney substance, the total of which, however is markedly diminished from the normal. Where it can be differentiated, the cortex of the kidney measures about 5 mm. in thickness. The striations are fairly distinct.

The left kidney is similar to the right. It is larger, however, and the cysts reach a diameter of 7 cm.

Blood vessels. Involving the arch of the aorta and scattered through the entire thoracic portion, are puckered scars. In these areas, the vessel wall may be quite thin, and on section red points make the scars

in the media characteristic. Superimposed upon this lesion, is the more usual arteriosclerotic process, which increases in intensity through the abdominal aorta and extends into the peripheral vessels, including those of the parenchymatous organs and especially the cerebral arterioles.

Heart. The heart is somewhat hypertrophied but not dilated. It weighs 400 grams. The pericardial and endocardial surfaces present nothing abnormal, and the valves are delicate. The wall of the left ventricle is decidedly thickened and measures 18 mm. The cavities of the ventricles are practically obliterated. The heart presents a picture of concentric hypertrophy.

Brain. (Following the usual custom, the head was injected with formalin before the brain was removed. The brain, however, was not equally permeated by the injection mass, and, consequently, had to be immersed in formalin for many days before it could be examined without harm.)

The blood vessels at the base of the brain are very prominent, and in many instances the lumina are definitely impinged upon by large, yellow plaques in the walls. This sclerotic process involves many of the intracerebral vessels. The pia arachnoid is delicate, and over the fourth ventricle alone, is a small amount of blood stained material.

Sections of the brain show a very extensive, fresh hemorrhage occupying all of the ventricles and involving the brain tissue around the right lateral ventricle. The hemorrhage extends through the parietal and occipital lobes and only a small rim of brain tissue separates it from the surface. On the left side there is a large hemorrhage in the parietal lobe just within the lateral ventricle. The basal ganglia are involved by these hemorrhages, and numerous, softened, yellowish foci within the basal ganglia indicate the presence of old lesions.

Microscopic notes. (Numerous sections were made of the kidney, and in some instances these were studied serially.) The cortical architecture is deranged by the presence of cysts of varying size. As a result, the sections included few areas where the gross architecture approaches normal. These show a slight diffuse increase in interstitial tissue with localized scars, usually beneath the capsule, in which glomeruli are hyalinized, tubules atrophic, and interstitial tissue richly infiltrated with mononuclear cells. Frequently an arteriole is involved in such a scar and shows great thickening and hyalinization of its wall. These scars are not particularly abundant even beneath the capsule, but occasionally radial scars extend from the region of the arcuate vessels even to the capsule. Where the cortex is uninvolved by such vascular

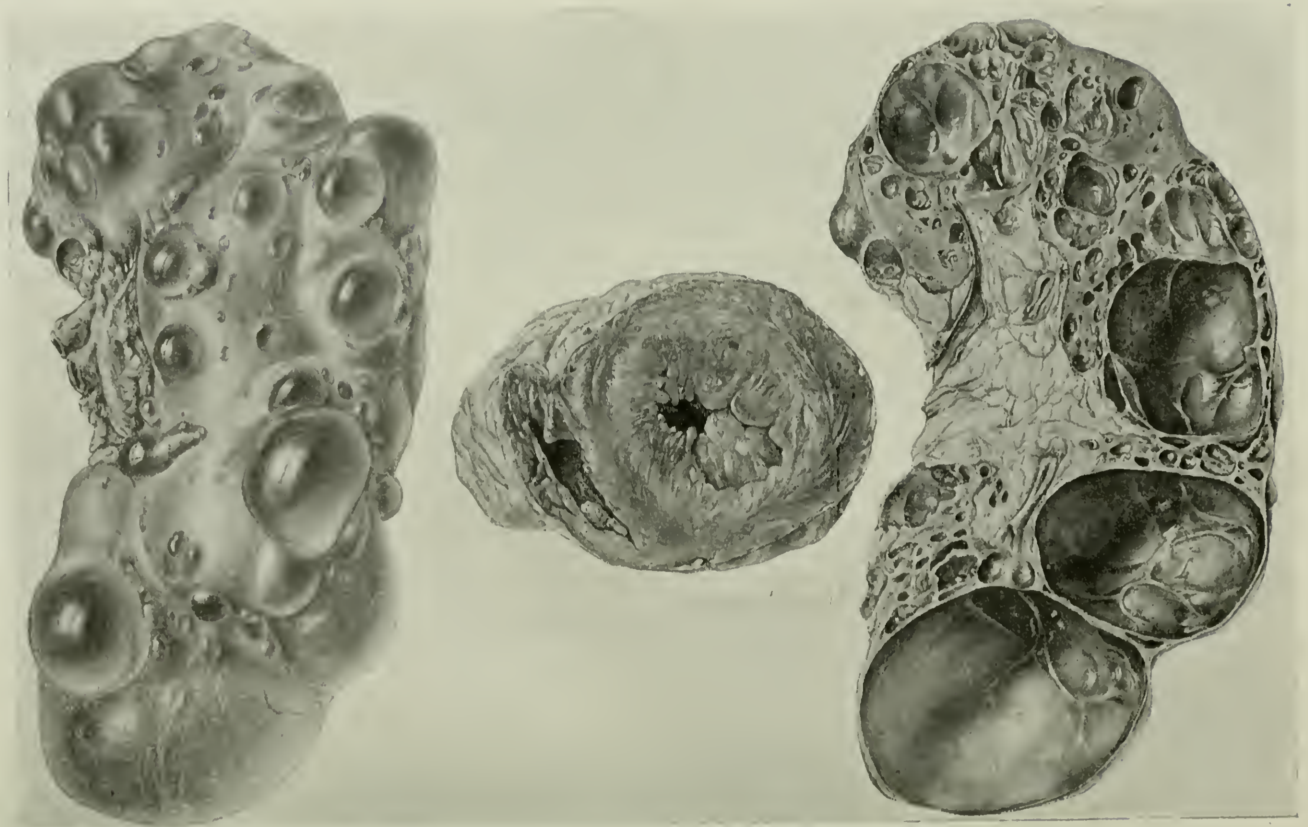


FIG. 1. CONGENITAL CYSTIC KIDNEYS AND CONCENTRIC CARDIAC HYPERTROPHY

A large number of variable sized cysts are shown both externally and on section of the kidney. Cross section of the ventricles shows the small cavity and the thick wall of the left chamber.

change or fibrosis, both the glomeruli and tubules are definitely enlarged, but otherwise bear the usual relation to each other. The glomeruli, aside from occasional hyalinization, show nothing abnormal and will not be referred to again. The tubules, on the other hand, show many interesting epithelial changes. These do not involve all of the tubules but are confined to the distal and proximal convoluted varieties and to the ascending loop of Henle. The most frequent change is found in the convoluted tubules. The epithelium is prominent and, with the low power of the microscope the nuclei appear extremely abundant. Frequently the epithelium is seen to be syncitial on careful examination, and as many as fifteen nuclei may occur in a single mass of protoplasm undifferentiated into individual cells. Such giant cells project into and may entirely occlude the lumen, even though it is dilated. Occasionally, too, the lumen of a tubule is occluded by a mass of cells each with its single nucleus, but otherwise resembling the giant cell picture above described. Such a mass may occupy only one section of the circumference of the tubule, and frequently, when the tubule is dilated—and such dilatation may cause the structure to be many times its normal size—the mass of epithelial cells projects into the lumen carrying with it the basement membrane, just as the hyperplastic epithelium of the thyroid in exophthalmic goiter causes invagination of the basement membrane of an acinus. Less often the basement membrane bends outwardly and the epithelium forms sprout-like masses which extend into the interstitial tissues. Such a sprout may appear as a sessile mass of cells projecting from the border of a tubule, or it may have a longer stalk and terminate in a structure resembling a typical tubule. The nuclei of these peculiar epithelial formations appear to stain more intensely with hematoxylin than those of the normal, because the abundance of nuclei in a local area makes them more conspicuous. They do not seem to be pyknotic nuclei, since their chromatin is definitely arranged upon a membrane and leaves clear zones between the individual chromatin pieces. The changes just described are more prominent in the convoluted tubules than in the ascending loops of Henle.

All gradations are found between the tubules showing slight hyperplasia and the well defined cysts, and it is difficult to conclude where proliferation of the epithelium and dilatation of the lumina of the tubules ceases and where cysts actually begin. Dilated tubules with numerous papillomatous proliferations may actually simulate the well known adenomata of the renal cortex. Degeneration in the hyperplastic epithelium of a tubule, and often of a dilated tubule, suggests that a re-

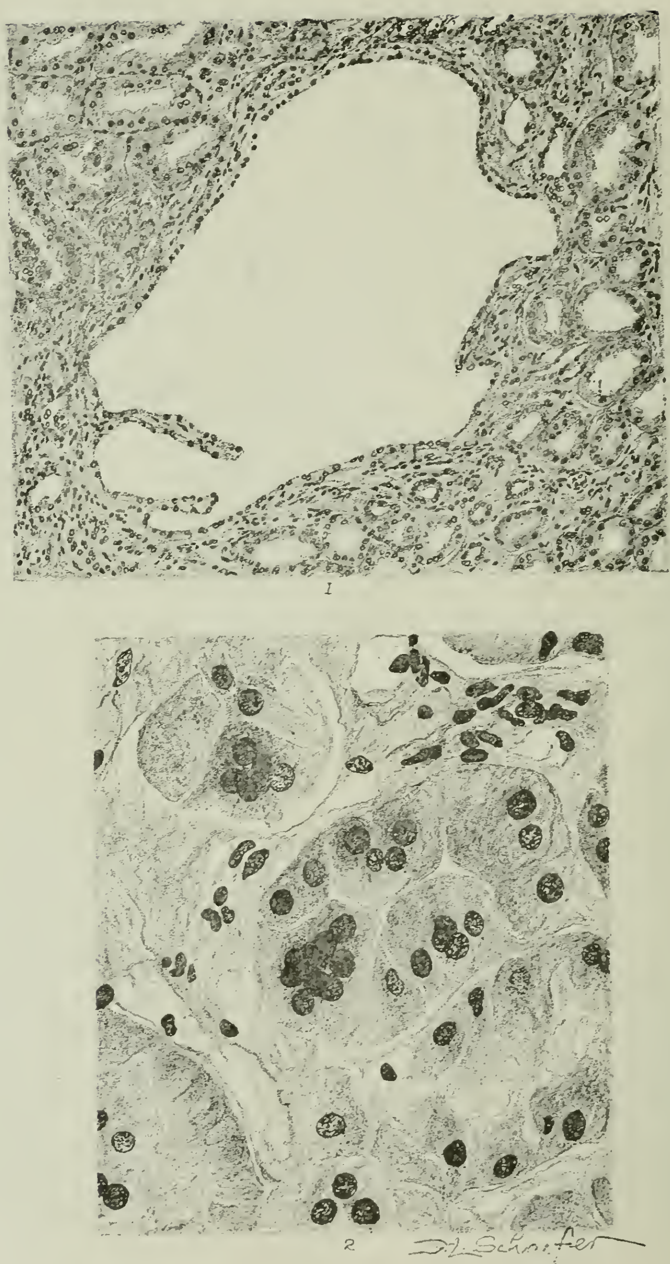


Fig. 2. (1) A small cyst lined by low cubical epithelium. (2) Many of the epithelial cells of the convoluted tubules are multinucleated.

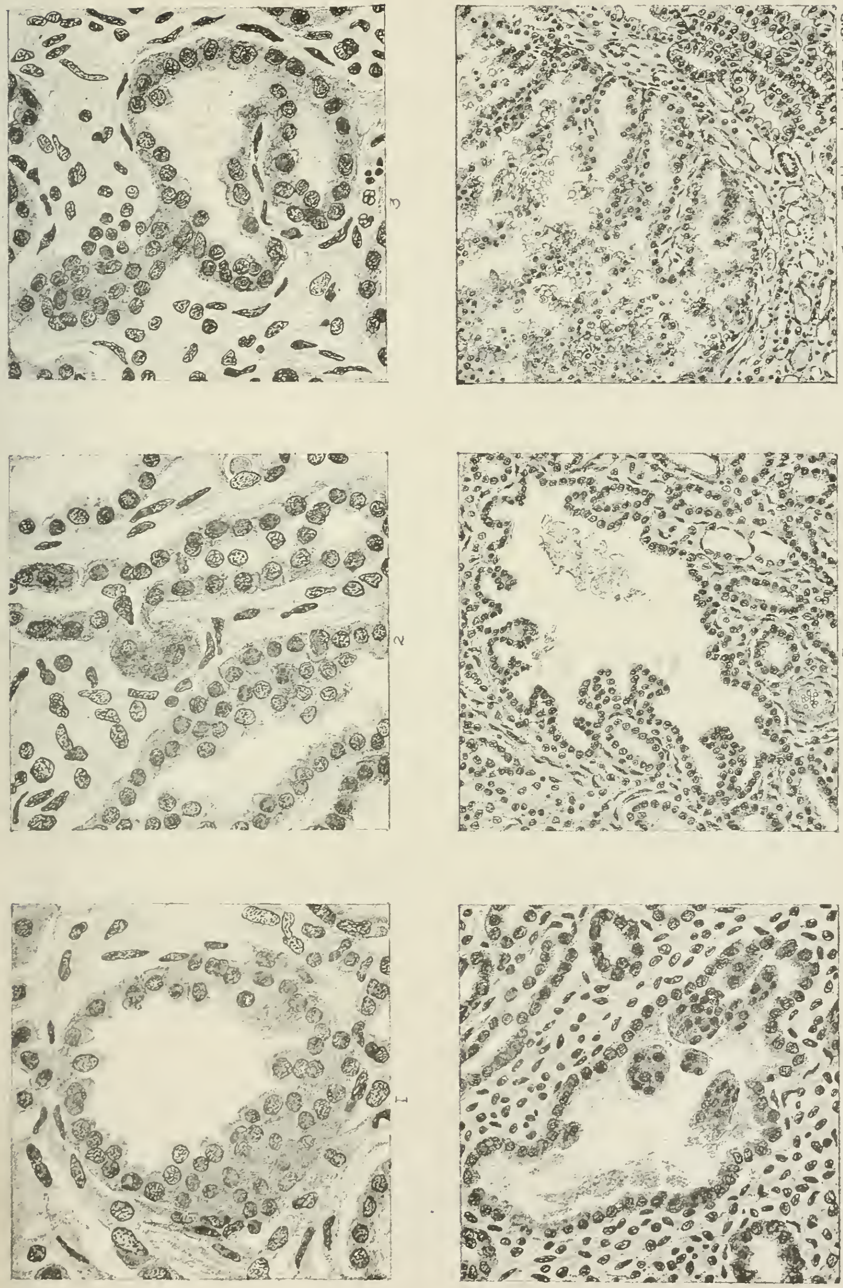


FIG. 3. (1) Proliferation of the epithelium in one sector of a dilated tubule. (2 and 3) Bud-like projections of the basement membrane and epithelium of a tubule into the interstitial tissue. (4) Proliferation of the epithelium of a dilated tubule to form villus-like syncitial projections seen on cross section. (5) Invagination of basement membrane with its lining epithelium. (6) A sector of a papillomatous cyst or adenoma of the renal cortex.

gressive metamorphosis may change the nature of the epithelial lining of such a tubule to that of a cyst with low or flat epithelial cells. Dilated tubules which approach the size of small cysts occur. They may be lined with cuboidal epithelium, but this may be replaced in local zones by multinucleated giant cells similar to those described above. The larger of the dilated cavities, which may be termed cysts, are lined by flat epithelium. At times this may be so low that it is made out with difficulty; elsewhere transition from flat to cuboidal epithelium occurs in an individual cyst. Still other cysts show masses of cells in one sector of their circumference, and occasionally mitotic figures occur in such foci. These masses may have a connective tissue core and project as papillomata of varying grades of complexity into the lumen of the cyst.

Case summary

An adult male, clinically suffering from cerebral hemorrhage shows at autopsy cystic kidneys of the congenital type. Hypertension, cardiac hypertrophy, vascular sclerosis, and cerebral hemorrhages are associated changes. The histological picture of the kidney is most interesting. It is characterized by extensive proliferation of the epithelium, particularly that of the convoluted tubules. The proliferated epithelium may occlude the lumina of such tubules either as a mass of individual cells or as a huge syncitial or giant cell structure. Frequently the tubules are dilated, and evagination with sprout formation into the interstitial tissues or invagination with papillomatous projections into the lumina of the dilated tubules occur. The line of demarcation between the tubules showing these changes and the cysts is not sharp. Although the vast majority of the cysts have low, flat, or cubical epithelial lining, cysts occur with epithelial masses on their walls composed of individual epithelial cells, multinuclear giant cells, and even papillary structures. Finally, structures are found similar to the usual adenomata of the cortex of the kidney.

DISCUSSION

Congenital cystic kidneys, as is well known, may attain such size during intrauterine life that their removal is necessary before delivery is possible. Not infrequently most of the substance of the kidney is occupied by cysts with extremely little functional tissue between them. Nevertheless, possessors of such

organs may attain adult life without knowing that there is anything amiss with their kidneys. Then, in the third or fourth decade, but frequently even later, evidence of renal disease appears, terminating with cardiac decompensation, uremia, or as in this case, with cerebral hemorrhage.

The condition may be hereditary. Dunger (5) shows that the tendency to inheritance is from father to son and from mother to daughter. Like other writers, he emphasizes the frequent occurrence of the lesions with other malformations such as hare-lip, hypospadias, rudimentary external genitalia, and with cysts in other organs, particularly in the liver. Lejars (9) found cysts of the liver in 16 of 60 cases. He considered the renal condition as a persistent congenital lesion of the type of "Epithelioma Mucoide." Coombs (4) in 10 of 58 cases, found 4 which had other developmental defects. The only anomaly found in the case reported in this paper was a small adenoma or rather cystic adenoma of the liver.

Many of the theories concerning the origin of congenital cystic kidneys are based upon microscopic study, and a brief review of these will aid in the interpretation of the histology of this case. Virchow (20) ascribed the cause of cyst formation to atresia of the tubules by irritation with uric acid and lime salts; later he concluded that intra-uterine papillitis causes obliteration of the collecting tubules, which in turn leads to cyst formation. This theory, however was shown by Busse (2) to be untenable. Sturm (19) believed that the cysts have their origin in bud-like, adenomatous processes. Chotinsky (3) considered the renal change a result of primary proliferation of both epithelium and stroma. Brigidi and Severi (1) observed epithelial proliferation, and concluded that through degeneration and change in the functional activity of the epithelium, small cysts are formed which grow by confluence. Coördinate proliferation of the connective tissue and tubules was observed by von Kahlden (7) who believed that the lesions are analogous to adenofibromata of other organs. Nauwerck and Hufschmid (12) described what they thought to be very early proliferation of the epithelium of the convoluted tubules. This, they believe, results in papillary growth and

terminates in simple or papillomatous cysts. von Mutach (11) also encountered proliferation of the tubular epithelium, but did not see the multinucleated or giant cell stage. He recorded two cases which he considered structural anomalies, and in both, atresia of the ureters was present. Reque (14), too, emphasized the proliferation of the tubular epithelium. In his two cases this was associated with old and fresh inflammatory changes in the renal parenchyma, and in one, degeneration in the center of proliferated epithelial masses suggested to him that this process might give rise to the cysts. Dunger (5) found that epithelial proliferation was not present in all cases, and concluded that it was secondary to primary error in development. Ribbert (15) also described epithelial proliferation in the convoluted tubules, and this was likened by Busse (2) to the epithelial proliferation he encountered in embryonal kidneys. Koster (8) upheld the malformation theory of the origin of congenital cystic kidney—failure of union between tubules and pelvis resulting in hyperplasia of the epithelium of the tubules with cyst formation. This view was supported by Shattock (18). Hildebrand (6) and Ribbert (15) modified it on the basis of the embryology of the kidney, and concluded that the cysts result through arrested development and failure of the glomeruli and tubules to unite with the straight tubules and pelvis.

This cursory review of the literature is sufficient to indicate the frequency with which epithelial proliferation in the convoluted tubules of congenital cystic kidneys has been observed. The majority of authors who have noticed these changes believe them to support the neoplastic theory of origin, and although the suggestion has been made, very little importance has been accorded the conception, that the epithelial proliferation is secondary to the cyst formation. The histology of the above case offers little in support of the malformation theory of origin of congenital cystic kidney, and the extensive epithelial changes would favor the neoplastic theory. On the other hand, few adenomata of long standing are so diffuse, and very few indeed show continued active proliferation, while compensatory hyperplasia in parenchymatous organs not infrequently results in a picture

analogous to that described above. In fact, epithelial proliferation, which is obviously an attempt to compensate, occurs in the kidney under some conditions and may result in pictures not unlike those found in the congenitally malformed organ. For example, Rössle (16) pointed out the similarity between the early stages of epithelial hyperplasia in congenital cystic kidney and proliferation in acute nephritis, associated with degenerative epithelial changes. The same author described epithelial proliferation with the formation of multinucleated giant cells and papillary projections into the lumina of the convoluted tubules, as well as sprout-like projections into the interstitial tissue in a case of chronic nephritis. Sacerdotti (17) found that when the blood of nephrectomized animals was transfused into a normal one, giving the kidneys of the latter double excretory work to perform, a great number of mitotic figures and atypical cell structures appeared in the epithelium of the tubules. Podwyssozki (13) described similar pictures in regeneration of the kidney after wounds. Thorel observed numerous mitoses, atypical cellular structures, epithelial sprouts, and occlusion of the lumina of the tubules by the proliferated epithelium in a man of seventy-one years whose kidneys were the seat of numerous infarcts. Similar epithelial changes were found by Wolff (21) eight, fourteen, and twenty days after resection of portions of the kidney. In a fatal case of eclampsia, Pels Leusden (10) also described epithelial hyperplasia of the convoluted tubules with giant cell formation, similar in all respects to that recorded by Nauwerck and Hufschmid cited above. It must be said, however, that this picture occurred only in that portion of the kidney thought to be the seat of malformation.

Thus, it has been pointed out that epithelial hyperplasia as a result of increased functional demands upon a portion of the kidney, may result in pictures not unlike those seen in the congenital cystic organ. It is interesting that in every case the convoluted tubules and the ascending loops of Henle, but more particularly the former, are involved. This may throw light upon the function of different portions of the kidney. It is generally assumed that congenital cystic kidneys may increase in size after birth,

and that several decades may elapse before large tumors result. No explanation has been offered for this subsequent increase in size by those who accept the malformation theory of origin. And cysts of the kidney, either single or multiple, are frequent accidental findings at the autopsy table without corresponding hyperplastic changes in the remainder of the organ. This fact suggests an explanation which is the more acceptable since it correlates the various types of renal change associated with cystic involvement. When the cysts are in sufficient quantity to stimulate hyperplastic compensatory change in the renal parenchyma, the lesion will be a progressive one, and cysts lined, entirely or in part, by high epithelium—even papillomatous cysts—will result from compensatory hyperplasia of the tubular epithelium.

SUMMARY

1. A case of congenital cystic kidney is presented where death occurred at the end of the third decade from arteriosclerosis and cerebral hemorrhage.

2. Epithelial hyperplasia of the convoluted tubules with giant cell formation, dilatation of the tubules, papillomatous infoldings, and bud-like sprouts characterize the histological picture.

3. The epithelial changes are not unlike the pictures that have been described for compensatory hyperplasia in the kidney.

4. It is suggested that the changes in the epithelium and of the tubules themselves are expressions of compensatory effort on the part of an organ whose functional capacity has been reduced by primary cystic change.

REFERENCES

(1) Brigidi, V., and Severi, A.: Contributo alla patogenesi delle cisti renale; Sperimentale, 1880, xlvi, 1.
(2) Busse, O.: Ueber kongenitalen Cystennieren; Deutsche med. Wchnschr., 1904, xxx, 130.
(3) Chotinsky, A.: Ueber Cystenniere; I.-D., Bern., 1882.
(4) Coombs: Polycystic disease of the kidneys; Quart. J. Med., 1909–10, iii, 30.
(5) Dunger, R.: Zur Lehre, von der Cystenniere, mit besonderer Berücksichtigung ihre Heredität; Ziegler's Beiträge, 1904, xxxv, 445.

(6) Hildebrand, O.: Weiterer Beitrag zur pathologischen Anatomie der Nierengeschwülste; Arch. f. klin. Chir., 1894, xlviii, 343.
(7) v. Kahlden, C.: Ueber der multiloculären Cystenniere und der Cystenleber; Ziegler's Beiträge, 1893, xiii, 291.
(8) Koster, W.: Nederl; Archiv. v. Genees en Naturk., ii, 779; iii, 103.
(9) Lejars, F.: Du gros rein polykystique de l'adulte; Thèse de Paris, 1888.
(10) Leusden, P.: Beitrag zur pathologischen Anatomie der Puerperaleklampsie; Virchow's Arch., 1895, cxlii, 1.
(11) v. Mutach, A.: Beitrag zur Genese der congenitalen Cystennieren; Virchow's Arch., 1895, cxlii, 46.
(12) Nauwerck, C., and Hufschmid, K.: Ueber das multiloculäre Adenokystom der Niere; Ziegler's Beiträge, 1893, xii, 1.
(13) Podwyssozki, W., Jun.: Experimentelle Untersuchungen über die Regeneration der Drüsengewebe. Zweiter Theil. Die Regeneration des Nierenepithels, der Meibom'schen Drusen und der Speicheldrüsen: Ziegler's Beiträge, 1888, ii, 1.
(14) Reque, H. A.: Congenital cystic kidney and liver (abstr.). Trans. Chicago Path. Soc., 1905, vi, 273.
(15) Ribbert, H.: Ueber die Entwicklung der bleibenden Niere and über die Entstehung der Cystenniere; Verhandl. d. Deutschen path. Gesells., 1899, ii, 187.
(16) Rössle, R.: Storungen der Regeneration von Nierenepithelien; Virchow's Arch., 1902, clxx, 375.
(17) Sacerdotti, C.: Ueber die compensatorische Hypertrophie der Nieren; Virchow's Arch., 1896, cxlvi, 267.
(18) Shattock, G.: Bilateral cystic disease of the kidneys in the new-born. Trans. Path. Soc. Lond., 1886, xxxvii, 287.
(19) Sturm, P.: Ueber das Adenom der Niere and über die Beziehung desselben zu einigen andern Neubildungen der Niere; Arch. D. Heilkunde, 1875, xvi, 193.
(20) Virchow, R.: Ueber kongenitale Nierenwassersucht. Ges. Abhandl. z. wissensch. Med., 1856.
(21) Wolff, M.: Die Nieren-Resection und ihre Folgen; Virchow's Arch., 1900, clxi, 36.

THE PATHOLOGY OF THE RENAL PELVIS IN TWO CASES SHOWING HEMATURIA OF THE SO-CALLED ESSENTIAL TYPE[1]

W. C. QUINBY

From the Urological Clinic of the Peter Bent Brigham Hospital

Renal bleeding is a matter of great importance to patient and urologist as well, for on the correct diagnosis and appropriate treatment of its cause depends the subsequent health of the individual.

As is well known cases occur occasionally in which bleeding from the kidney is the only symptom or sign which can be found. Such cases are always baffling because the cause of the bleeding being unknown any treatment must of necessity be of the expectant variety. The cause not being clear such terms as "idiopathic" or "essential" hematuria have come into use. Such terms of course merely mean "cause unknown" and should therefore be avoided if possible.

It is therefore with the hope of throwing further light on such types of hematuria that the following cases are reported:

Case I. A negress twenty-one years of age entered the Peter Bent Brigham Hospital on May 31, 1919, complaining of hematuria and pain in the abdomen. The family history was negative. Four months before entrance she had had a definite hemoptysis and at present physical examination of the lungs shows a healed or quiescent tuberculosis of the apices. Patient had been married three years and had always been well except for a persistent leucorrhea since that time. She has had one child two and a half years ago. Since the birth of this child she has been subject to pain in the right flank said to be present a good part of the time but only troublesome during an occasional rare attack when it became very severe. The pain has never radiated to other portions

[1] Read at the Meeting of the American Urological Association, New York, March, 1920.

of the body. During the past month the urine was a port wine color and frequently contained small clots.

Examination showed a normal temperature, pulse and respiration. The abdomen was normal and without tenderness anywhere. Analysis of the urine showed a red color due to much gross blood and a few small clots. The reaction was neutral; specific gravity 1.012; albumin a trace, and sugar absent. The microscope showed a heavy sediment of red blood cells, with practically nothing else visible except a rare

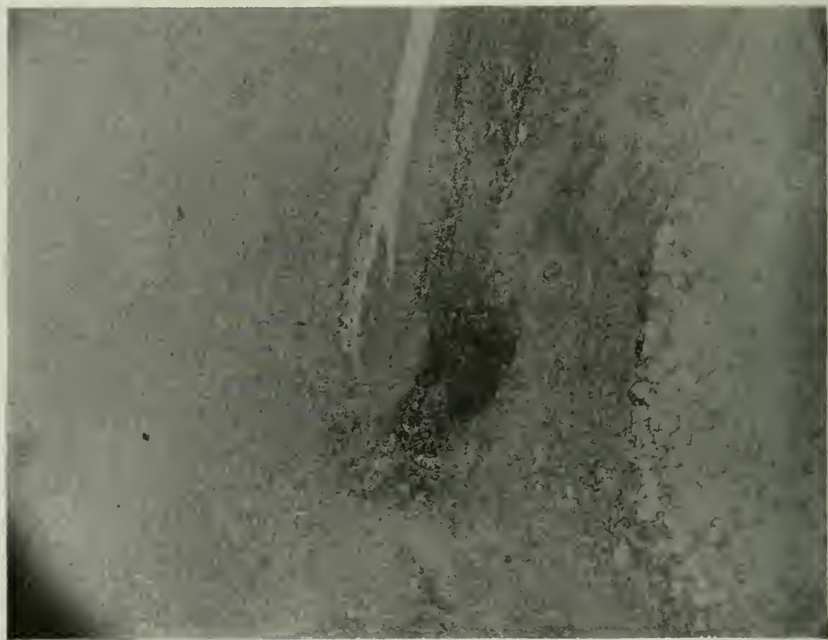


Fig. 1. Portion of Wall of Pelvis with Renal Papilla

Note area of hemorrhage. Low power. Case 2

white blood cell or epithelial cell. Hemoglobin 65 per cent; white blood cells 6500; blood pressure 130 systolic; 62 diastolic.

On June 2 cystoscopic examination showed a normal bladder containing a soft, round, red mass made up of coagulated blood. From the right ureteral orifice which was normal in outline, there came blood. From the left side the urine was free from blood. The phenolsulphonephthalein estimation from the left side was normal; from the right

side it could not be read on account of the blood. The x-ray plates showed no shadows in any part of the urinary tract that could be interpreted as stone. The calyces of the right kidney were small and tapering and somewhat drawn out. There was a duplication of the pelvis, but no other abnormality could be seen.

At operation on June 6, 1919, the kidney was found well up under the ribs and not unduly movable. There was no perirenal sclerosis of the fatty tissue. The kidney itself was of normal size and consistence,

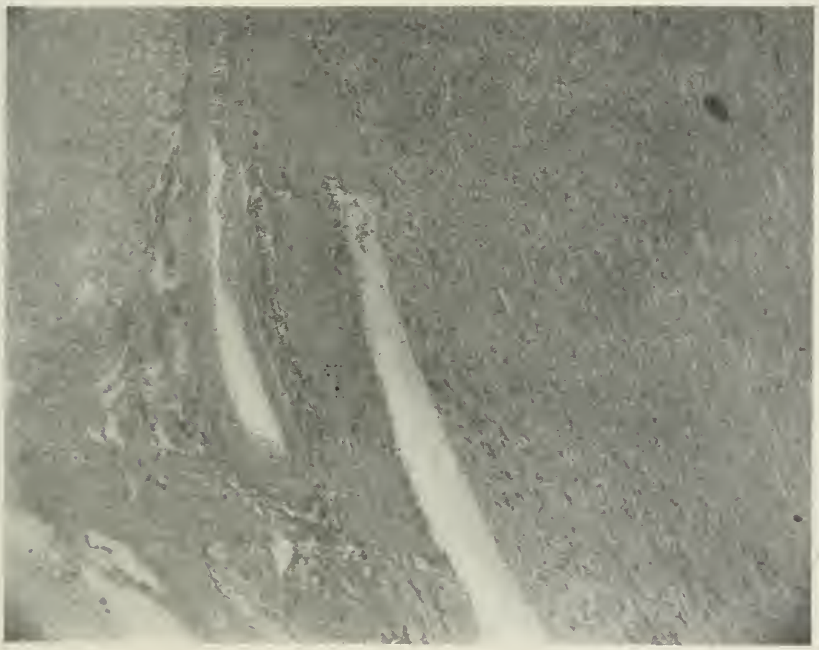


Fig. 2. Same Area in Case 1

Shows less hemorrhage free in tissues but many dilated capillaries engorged with blood in the papilla.

with no evidence of stone. The ureter and pelvis were also normal on palpation. Except for extreme congestion of its surface the kidney seemed normal. It was removed, however, because of the history of persistent hematuria.

The patient made a good recovery and was discharged well on the twenty-second day after operation.

Case II. A Greek tanner aged thirty-eight entered the Peter Bent Brigham Hospital on May 28, 1919, complaining of hematuria. The family history and past history were both negative. The present illness began a year and a half before entrance when the patient first noticed blood in the urine. This continued to be present constantly except after the patient had taken a large quantity of water. The patient also had had a pain across the lumbar region, accentuated on the left side, which he said had been present every day for eight or ten

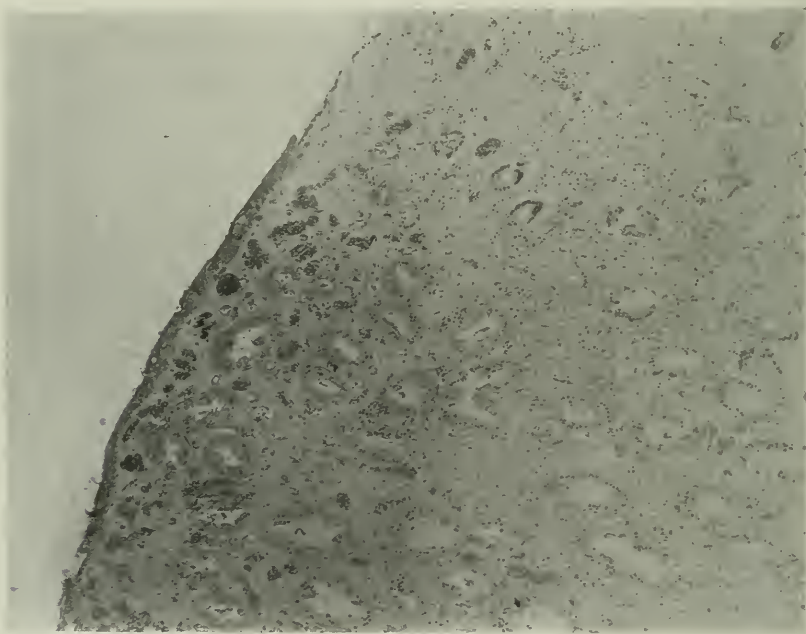


Fig. 3. Higher Power of Renal Papilla in Case 1

Note extensive capillary network beneath mucosa

years. This pain was not severe, only just enough to bother him. There had been no loss of weight and his general health and strength had been excellent. The patient has had no venereal disease.

There was slight tenderness in the left costovertebral angle, and the lower pole of each kidney was palpable. Otherwise the physical examination was normal in all respects. The blood pressure was 122 systolic, 88 diastolic. Urine analysis: Red, cloudy, slightly alkaline; spe-

cific gravity, 1.020; slight trace of albumin, no sugar. The microscope showed red blood cells; no casts or crystals. Phenolsulphonephthalein test, 60 per cent in two hours. Cystoscopic examination showed a normal bladder with a capacity of 350 cc. A brilliant efflux of red blood came from the left ureteral orifice. The urine from the right orifice appeared normal. Catheters passed on each side for 30 cm. The renal function on the right side was 10 per cent of dye in fifteen minutes. Bacteriological examination of the urine showed no tubercle bacilli and cultures were sterile.

X-ray report. The right kidney outline was fairly well shown. It was apparently normal in size and position. The left kidney outline was somewhat indistinct and there was a suggestion of enlargement in the lower pole. Pyelograms showed nothing definitely pathological.

At operation on June 2, 1919, the kidney appeared entirely normal. There were no unusual adhesions to the surrounding tissues, or any irregularities in the kidney itself, either in size or surface. Because of the profuse hematuria, however, it was deemed wise to remove the organ.

The patient made a normal recovery and was discharged on the sixteenth day after operation.

Gross description of kidneys

Case I. The kidney weighs 170 grams, and measures 12 by 5 by 2.5 cm. There is slight fetal lobulation. The kidney tissue is normal in appearance. The mucous membrane of the pelvis of the kidney is studded with numerous deep red, punctate areas which are so abundant about the orifices of the calyces as to form bright red, velvety zones several millimeters in width. Dissection of the calyces shows that this condition is widespread, involving every calyx, and in a few instances the whole of the mucosa of the calyx is bright red and velvety. Attached to the apices of a few pyramids are minute, soft, red clots. On further section of the kidney, minute, punctate, dark red areas, evidently hemorrhage, are found in a few pyramids close to the apex. In addition, a few pyramids show deep red and delicate lines radiating upward from the apex.

Case II. The kidney weighs 182 grams, and measures 12 by 6 by 3.5 cm. It is slightly diffusely reddened and edematous. The cortex averages about 12 mm. in width. The glomeruli are quite prominent as slightly reddened dots. Capsule strips easily from a smooth, dull

red surface. The medullary markings appear normal. The pelvis has a dark red, hemorrhagic appearance. A greyish white exudate on the surface can be stripped off. The calyces are considerably injected at the point where the pyramids abut. There is no evidence of tumor.

The pathological examination of these kidneys was made by Dr. E. W. Goodpasture, Assistant Professor of Pathology in the Harvard Medical School, who has been kind enough to give me the following opinion:

The sections were taken from kidneys removed at operation for more or less continuous renal hemorrhage. The sections available for study show the two cases to be similar in respect to the source of the hemorrhage. Careful study of several specimens shows no evidence of injury or the presence of hemorrhages in the interstitial tissue or in tubules of the cortex or pryamids. In each case the parenchyma of the two kidneys appears in sections to be essentially normal. The source of the hemorrhage in each case is obviously from the pelvis and from the tips of the pyramids. In each instance hemorrhages are present within the peripelvic tissues, often occurring just beneath the epithelium where for considerable distances the epithelium has been elevated by a layer of extravasated blood. In the first case, there is no evidence of inflammatory reaction in the tissues of the pelvis or about the blood vessels. The hemorrhages are represented by extravasations of red blood cells from thin walled, dilated capillaries and veins. Just beneath the epithelium of the pelvis unruptured, large, thin walled, vascular channels can be seen, evidently considerably distended. Even larger arteries may show extravasated blood external to the adventitia. These hemorrhages appear to be fresh. There is no blood pigment in the tissues, no reaction on the part of the fixed tissue cells, and no evidence of phagocytosis. The vascular channels between the collecting tubules of the pyramids, especially nearer the apex are very wide, often irregular and tortuous, giving the appearance of vascular sinuses rather than veins or capillaries, and these sinuses are distended with blood. Their walls are thin and delicate and there is an absence of fibrous tissue proliferation throughout this region. Careful examination of the larger vessels, both veins and arteries, reveals no obvious abnormality.

The lesion present in case II, although occurring in the same situation and resulting in similar hemorrhages is pathologically of a different nature than that of case I. Here one finds in addition to hemorrhages

beneath the epithelium of the pelvis and in the peripelvic connective tissue, distinct inflammatory reaction and evidences of vascular injury. At the margin of some of the hemorrhages one finds focal accumulations of polymorphonuclear leucocytes, fibrin, serous exudate and proliferation of fibroblasts; mitoses being not infrequently seen. In such areas one also finds small foci of necrosis in which a few leucocytes and mononuclear cells have undergone disintegration. In addition there are veins, in and about the wall of which are interlacing bands of fibrin

Fig. 4. An Enlarged Venous Sinus from Area Near Tip of Papilla
Note septa similar to those seen in true telangiectasis. Case 1

so that the space between is outlined by this fibrin network. Within the pyramid near the apex one can also find here and there small foci of necrosis about which there are a few polymorphonuclear leucocytes and also numerous punctate hemorrhages. The blood vessels at the periphery of the peripelvic tissue show a considerable infiltration of small lymphocytes about their walls. In this kidney also the hemorrhages appear to be fresh and there is no evidence of blood destruction.

such as the presence of pigment or phagocytosis. The larger blood vessels show no obvious abnormality.

In attempting to formulate an opinion as to the nature and cause of the lesions described one finds considerable difficulty in discovering an adequate explanation for them. In the first case vascular distension, rupture and hemorrhage is the essential feature. One can conceive therefore that the hemorrhage in this case might be due either to mechanical rupture of blood vessels through distension of otherwise normal channels, or that the rupture was due primarily to injury of the thin vascular walls from some circulating injurious agent. In the second case one cannot reasonably explain the lesion on the grounds of pure mechanical rupture since an inflammatory reaction is very obvious. Careful search within the area of inflammatory change has not revealed the presence of bacteria, yet there is distinct evidence of vascular injury

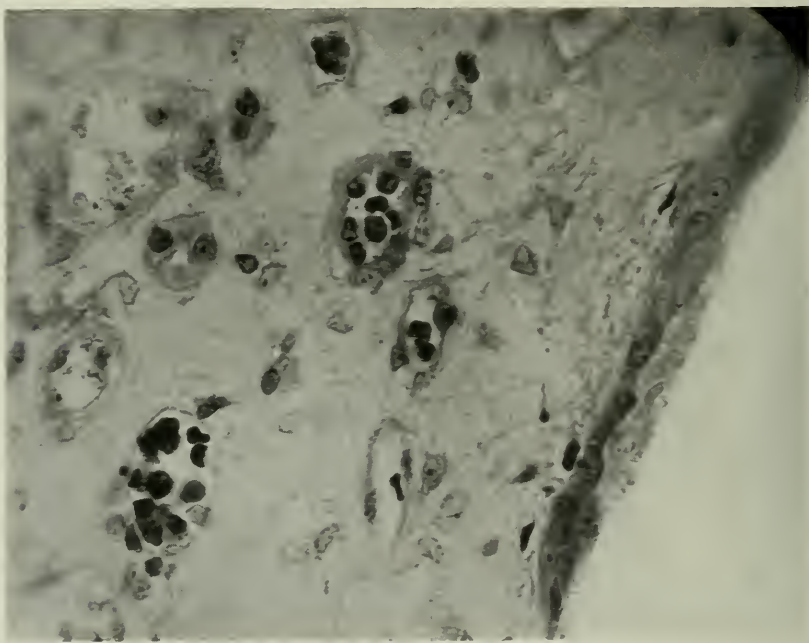


Fig. 5. High Power of Renal Papilla; Case 2

Note engorgement of capillaries and edema of peritubular tissue with occasional lymphocyte about the vessels.

which may possibly be explained on the assumption of the presence of bacteria within the lesions. The type of inflammatory reaction certainly indicates the presence of a local injurious agent, which it is not necessary to assume for the first case.

It is thus seen that although the cause for this condition is not clear the location of the hemorrhage just under the epithelium of the pelvis and to a less extent in the substance of the papilla itself makes a definite and clear cut picture.

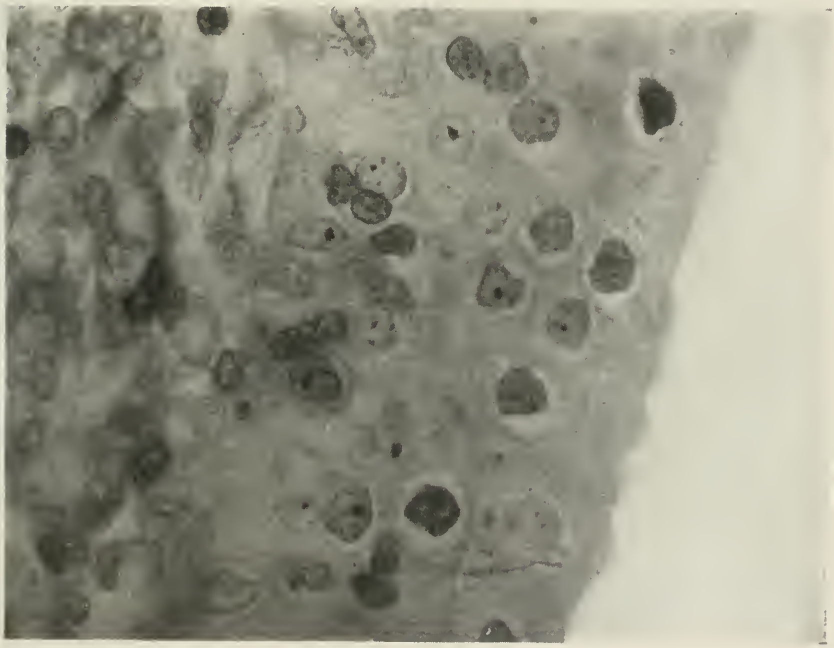


FIG. 6. HIGH POWER OF PELVIC EPITHELIUM; CASE 2

The epithelium rests on a dense layer of extravasated red blood cells a few of which are seen penetrating the epithelium by diapedesis.

Whether the condition has been caused by soluble toxins which have chosen these areas of the kidney as their point of elective action or whether it is due to infection by bacteria is not to be determined. A most careful search of the material at hand failed entirely to demonstrate bacteria, even in case two which showed evidences of inflammation.

A search of the literature has brought forth the fact that in small pox, hemorrhage is not infrequently seen just in this area. In this instance the causative agent is presumably a toxin. In 1916 Payne and MacNider[2] described a condition similar to that found in our cases. They ascribed the hemorrhage to over-distension of the venous plexus of the renal papilla caused by infection, with exudation and pressure on the veins just at the base of the pyramid. Although there is considerable similarity between their illustrations and the condition which I am describing, in neither of my cases was there any evidence whatever of inflammation at the base of the pyramids. On the contrary, all the renal tissue was normal except in the immediate vicinity of the areas of hemorrhage. In these instances, therefore, their interesting assumption is not tenable.

It is evident that careful observation of many more similar cases is necessary before their explanation will become clear.

In regard to treatment of this condition I can only suggest that it would seem to be a type of lesion which might be expected to respond to pelvic lavage with some such caustic as silver nitrate, if this be used of sufficient strength to cause a definite chemical reaction. Indeed it would seem probable that in those reported instances where hematuria has ceased after such lavage this condition described here was present. In view of the location of the source of the bleeding such a procedure as nephrotomy would certainly seem ill advised.

[2] Jour. A. M. A., September 23, 1916, lxvii, no. 13.

IDIOPATHIC GANGRENE OF THE SCROTUM[1]

ALEXANDER RANDALL

Philadelphia

There is no better way to bring quickly to your attention the picture of the condition I am about to describe than to cite the history of a typical case.

Case 1. Albert M., age thirty-nine, a well developed and normal negro, arose on the morning of January 2, 1920, in his usual good health. His occupation was that of chauffeur in a private family, driving only pleasure cars. About 3.00 p.m. on the above mentioned day, while driving a limousine in the city, he was seized with a chill which lasted half an hour, to be followed by a severe headache and fever. By 7.00 p.m. he was semi-delirious, and remembers but little of what transpired during the succeeding days. His physician was called and found his temperature to be 101°, and with a few râles in his chest naturally suspected grippe. An expectorant of ammonium carbonate and heroin was ordered, also a pill of camphor, quinine and Dover's powder. The following evening the evidence of pain first attracted his wife's attention to the genitalia, and his physician on the following, or third day of his illness, found the penis swollen to double its normal size, intensely inflamed, though neither indurated nor edematous. The swelling appeared to be proceeding from the distal end towards the pubis, stated his physician, and on reaching the hair margin it spread rapidly to and involved the entire scrotal wall. This scrotal involvement took place on January 6, 1920, the fourth day of the illness. An application of lead water and laudanum was applied to the tumefaction of the scrotum, while the condition on the penis, of little longer duration, had already developed a necrosing area near the prepuce, to which was applied aristol powder, and later zinc oxide ointment. The following day the scrotal swelling assumed the size of an infant's head, and was extremely painful; the patient suffered repeated chills, associated

[1] Read before the American Urological Association, meeting in New York City, March 23, 1920.

with profuse sweats and fever. Headache persisted and there were generalized pains over the chest and extremities. As the patient's condition seemed critical he was moved to a nearby hospital on January 7, and on the following day, the sixth of his illness, he was transferred to the Philadelphia General Hospital. The only other application to the local condition was olive oil and at no time was heat or an escharotic used. Urination remained undisturbed and normal. I first saw the patient on January 9, at which time the penile swelling had already become gangrenous and an enormous slough was separating, while at the bottom of the scrotum, on either side, were two areas, each about 5 by 10 cm. in extent, where the skin was drying and puckering, blacker than the surrounding tissue, and extremely soft and boggy to the touch, the whole emitting a repulsive, fetid odor. The stench was horrible. Pain, on the other hand, was almost absent and on palpation there was a distinct emphysematous crepitation throughout the entire scrotal tumefaction.

I was anxious that the condition could be shown the student class on January 12, but by that day's arrival the necrotic mass had separated, the line of demarcation forming just below the scrotal attachment to the body, and three-fourths of the scrotal wall had sloughed off.

Such is the typical history and clinical course of this unusual genital affection which, though not new to the world's literature, is however one so consistently omitted from our text books that I considered it worthy of your attention at this time.

In peculiar contrast to the apparent literary silence has been my experience while on service in the Urological Wards of the Philadelphia General Hospital, where the condition has been repeatedly seen year by year. Possibly the reason for this experience lies in the fact that the average smaller hospital is unwilling to admit such cases to its wards, and speaking from the experience of Philadelphia, it is usual there for all such cases to gravitate, more or less automatically, to the wards of the larger municipal institution.

The most marked feature of this condition, so well exemplified in the case above cited, is the explosion of the phenomena in the midst of apparent perfect health. The sudden onset is only equalled by the rapidity of the ensuing symptomatology; chill, fever, prostration, pallor, rapid pulse, even nausea, vomiting,

and delirium, proceed and accompany the development of the scrotal swelling. This local manifestation within twenty-four to forty-eight hours attains the size treble that of normal, is intensely painful, tense, glassy, reddened, and hot to the touch, showing all the evidences of an acute infection. This stage does not last long, and within another twenty-four or forty-eight hours, inspection of the lesion finds it pitting on pressure, the surfaces greasy, exuding, duller red in color, and, at the most dependent portions especially, the dermal surfaces showing moist desquamation, while the odor of mortification, so repulsive yet so characteristic, is present.

Palpation of the scrotum just before the gangrene sets in and even later in well marked cases, elicits in a large proportion an emphysematous, crepitant sensation, leaving no doubt that the tissues contain gas.

The subsequent course is of equal interest. The gangrene usually spreads rapidly upward in all directions. In some cases several patches of gangrenous tissue appear simultaneously on different portions of the scrotum varying in size from half a dollar to areas treble that in size. In other cases the first point of involvement is on the shaft of the penis, and this area continues to show the most advanced lesions, though scrotal swelling has rapidly followed. As a rule with the formation of the gangrenous slough the systemic symptoms begin to ameliorate and unless toxemia has been very marked the patient shows definite improvement and can be expected to recover. Shortly after the gangrenous slough softens a typical line of demarcation appears showing the limitations to which the process will extend. The area usually involved is the scrotal wall with a sloughing of three-fourths of the entire sac, though cases have been seen that on the one hand have been limited to one side of the scrotum only, and yet others in which the involvement rapidly spreads to the groins, and over the pubes to the lower abdominal wall, extending as high as the umbilicus. Peculiarly the perineum seldom suffers and I have found but one case in the literature wherein it was reported that the anal margin and part of the rectal wall came away with the slough. Likewise the skin of the thighs is

apparently not prone to suffer from the spread of the gangrenous process.

About three days from the time that the line of demarcation shows the limits of the gangrenous process, a massive, stinking, slough separates. Where the scrotum is involved the skin, subcutaneous tissues, fascia, dartos, and all the structures of its wall, come away in a stringy, fetid mass. The testes, bared to their tunica vaginales, hang suspended by their cords, shamefully exposed, though remarkably free of gangrene, inured and oblivious to their new surroundings (or possibly I should say lack of surroundings), and can be handled freely without causing the slightest discomfort. I have seen but one case where the testis, or its intimate covering the tunica, became involved in the destructive process, and in this patient only a small portion of the tunica vaginalis, 2 by 3 cm., was destroyed, the gonad itself being bared, though uninvolved. In the literature I have found no case where testicular involvement caused gangrene of these organs.

With the separation of the slough sharp secondary hemorrhages frequently occur, where bleeding might be excessive unless watched for and early ligation applied. In our wards the trained male nurse has undoubtedly saved life in several instances by close watching and prompt attention to this point.

Once the gangrenous tissues have been removed, underlying them is found a healthy surface and granulation starts with surprising rapidity and energy. Strange as it may seem scrotal regeneration can be expected and with careful nursing and dressing a new scrotum can be made to enclose the testes in type and character but little different from its predecessor.

Apparently first accurately described by Fournier in the Semaine Medical in 1883–1884, the literature contains scattered reports that were ably collected and grouped by Whiting in 1905. Whiting's article covers the entire subject of scrotal gangrene and he divides his cases into five groups as follows:

Group 1. Gangrene due to the action of bacteria "either through 'the specific chemical substance which they liberate or as the result of vascular obstruction due to the inflammatory process to which they give rise.' (Warren.)"

Group 2. Gangrene due to interference with the nutrition of the part by obstructing the circulation, the causes being other than micro-organismal.

Group 3. Gangrene due to direct mechanical or chemical action.

Group 4. Gangrene due to thermal agents.

Group 5. Cases in which the gangrene is caused by injury of the so-called trophic nerves.

While writing on the entire subject of gangrene of the scrotum Whiting found but 93 reported cases in the literature of that date (1905) and it is obvious from his article that the type of case to which I have drawn your attention includes only those that he classifies under group 1, herein giving a total of 36 instances so recorded, in eight of which death occurred, a mortality of 22.2 per cent.

In 1911 Coenen and Przedborski likewise cover the general subject of penile and scrotal gangrene dividing their 203 cases collected from the literature into four groups; viz.:

Group 1. Those secondary to a generalized infectious disease or circulatory disturbance.

Group 2. Those secondary to urinary extravasation.

Group 3. Those secondary to mechanical, chemical, or thermal agents.

Group 4. Those due to a local "inflammatory-infectious" process.

Here again the type of case to which I have referred occurs only in their fourth group, wherein they report 145 cases, 32 of which ended fatally, again a mortality of 22.1 per cent.

In the literature since Coenen's report in 1911, I have been able to find but two cases reported, those of Zehr, and of Thibault and Schulmann. Unfortunately because of the war's interruption it has been impossible for me to obtain for review articles by Kyrle, Lequeu and Bok (see bibliography).

In reviewing the 147 case histories since 1904 from the wards of the Philadelphia General Hospital, wherein gangrene of the genitalia was the diagnosis, I have been able to tabulate 16 cases that I believe to be this pure type of spontaneous gangrene of

the scrotum, uncomplicated by any of the other etiological conditions in the grouping of the lesion as accepted and outlined by Whiting and Coenen.

Case 2. P. F. R. (B.2492). Age fifty-eight. White. Clerk. Admitted October 28, 1918. Onset very acute. The patient awoke on the morning of October 14, with a very large, distended, swollen and painful scrotum. The skin over it was tense and discolored a dusky red for the two following days. It then ulcerated on the right side whence a malodorous and purulent fluid escaped. The slough came away the following day leaving the testicle exposed. There has been no pain since the first few days. He had suffered no trauma, never any difficulty of urination, and at no time has any urine passed through the scrotal wound. Only application to scrotum during the fourteen days between onset and hospital admission has been vaseline. Physical examination: Gangrene has involved only the right side of the scrotum, testis exposed; lesion now clean and good granulation present. On December 2, 1918, lesion almost healed and patient discharged from the hospital. Nothing but local dressing done to the lesion.

Case 3. P. H. (B.595). Age sixty. White. Laborer. Admitted January 31, 1917. Onset two weeks ago with sudden painful swelling of the scrotum. Has had no urinary troubles. Physical examination: Scrotum greatly swollen, edematous, and gangrenous in lower half. Temperature 102°. Pulse 130. Scrotal walls incised and drainage established. Line of demarcation formed and slough separated exposing both testicles. Healing by granulation ensued, new scrotum formed, covering both testicles successfully. Discharged March 14, 1917. Cured.

Case 4. T. R. (B.612). Age forty-four. Colored. Laborer. Admitted February 25, 1917. Onset ten days before admission when scrotum suddenly swelled to about the size of a man's head. Was very painful and tender to touch. Eighth day from onset lower part of scrotum became gangrenous. Physical examination: Lower half of scrotum entirely sloughed away and both testicles exposed. Temperature 103.8°. Pulse 120. Patient profoundly toxic. Condition remained septic during entire stay in hospital, growing weaker and refusing nourishment. No other lesion detected. Under treatment the scrotal condition was granulating satisfactorily and all gangrene stopped. Patient died in profound toxemia on March 20, 1917.

Case 5. A. C. (B.344). Age fifty. White Barber. Admitted December 5, 1916. Patient admitted irrational and delirious, frequently jumping out of bed. Only history gives onset seven days before. Physical examination: Penis swollen, congested, ecchymotic with several places where the skin is broken with bloody serum exuding. Scrotum very large, boggy, skin black in places and evidently necrotic with a similar bloody serum exuding. Patient incontinent of urine and feces. Temperature 101°. December 11, mental condition slightly improved, patiently very toxic and refusing nourishment. Temperature typically septic, with pulse up to 140. Gangrenous tissue of two-thirds of scrotum and the entire shaft of the penis has sloughed off leaving good granulating surfaces. Testicles exposed but uninvolved. General condition remains unaltered. Patient died December 26, 1916, in profound toxemia.

Case 6. W. C. (A.8991). Age forty-four. Colored. Barber. Admitted April 27, 1915. Onset four weeks ago while in perfect health, with slight swelling in the scrotum. It increased in size becoming painful and tender. Had repeated chills, almost daily since onset. Condition in scrotum has been growing progressively worse and patient has had to be catheterized three times since onset of illness. Physical examination: A slight discharge from the meatus with marked swelling of the scrotum, measuring 8 by 6 inches. Tissue of the scrotal wall highly inflamed, edematous, with occasional crackling felt in the tissues on palpation. Slight fullness in the perineum. Catheterized with ease and foul putrescent urine obtained. No stricture. Patient having repeated chills, temperature as high as 103.8.° Pulse 130. Scrotum incised and through and through drainage established. Subcutaneous tissues gangrenous and gas containing. Entire scrotal wall sloughed away, testicles exposed. Successful healing by granulation followed. Discharged, cured, on June 1, 1915.

Case 7. T. F. (A.8746). Age thirty-nine. White. Electrician. Admitted November 21, 1914. Was perfectly well five days before admission. Had no urethral discharge, no sores about genitalia, could always pass his urine without difficulty and denies venereal disease. Suddenly developed pain in the right inguinal region, followed by chill and fever. Penis became painful and swollen. Physical examination: Penis very edematous, dusky red in color, with several patches of dark reddish-blue collections under the skin. Scrotum swollen to double its normal size, red, tender, with areas of inflammation extending up over both inguinal regions and a little over the pubes and lower abdominal

wall, with no well marked line of demarcation as yet formed. Suggestive crepitation over root of penis and adjacent abdominal wall. Temperature 104°. Multiple incisions made, with gas exuding from the subcutaneous tissues on each cut. Subcutaneous tissues all gangrenous. Entire scrotum sloughed away; testicles exposed. Uninterrupted healing. Discharged, cured, January 23, 1915.

Case 8. G. M. (A.8609). Age fifty-seven. White. Admitted November 5, 1914, to the nervous wards. History of onset two weeks ago with an attack of vomiting which has continued at least once a day ever since. Two days ago he was too weak to walk and the day before admission had a chill. Scrotum started to swell five days ago. Physical examination: Heart laboring with frequent intermissions. Pulse 140, loud blowing systolic murmur. Abdomen tense, no tenderness, no palpable mass. Irregular brownish macular areas 2 by 4 inches over lower abdomen. Scrotum double normal size, boggy, dull on percussion, markedly inflamed, the area of inflammatory involvement extending up left inguinal region and over lower abdomen. Temperature 103°. Passes flatus and feces, bladder catheterized and found empty, no stricture. Transferred to the surgical wards November 7—diagnosis scrotal cellulitis. Transferred same day to the urological wards. Condition very weak. Lower abdomen, scrotum, and perineum red, swollen, and on palpation crepitation is felt everywhere, even extending beyond the line of redness on the abdominal wall. Incision was made in each side of the scrotum and in the left groin; gas exuded from subcutaneous tissues, and all subcuticular structures gangrenous. Drainage. Patient died November 8, 1914.

Case 9. S. S. (A.8318). Age twenty-four. White. Laborer. Admitted April 13, 1914. Patient suffering from chancroidal ulceration of the prepuce. Three days ago he had a severe chill which was repeated several times during the day and at the same time the scrotum began to swell causing burning pain. Physical examination: Penis presents ulcerations about the prepucial margin and is markedly swollen throughout. Scrotum is very swollen, red, and generally inflamed. April 14, condition of patient is worse; redness and inflammation have passed upward onto the abdominal wall with remarkable rapidity. Patient prostrated and sweating profusely. Temperature 103°. Pulse 100. Two-inch incision made in one side of scrotum, high up and drainage put in. (This was done under cocaine anesthesia, was too small and too superficial. Patient was not benefited, and no gangrene was noted.) April 16, condition aggravated; lower half of scrotum has

sloughed off. Penis markedly enlarged, swollen, and beginning gangrene evident. Inflammation extends up upon the abdominal wall to within 2 inches of the umbilicus. Under ether anesthesia free incisions were made and through and through gauze drainage placed: also several incisions in the sides of the penis. All incisions were followed by the escape of quantities of watery pus and gas. Crackling crepitus distinctly noticed in the tissues to the limit of the inflammation. Immediate improvement. Free sloughing of all gangrenous subcutaneous tissue. Healing progressed rapidly. Diischarged, cured, June 18, 1914.

Case 10. J. H. (A.7528). Age forty-nine. White. Shoemaker. Admitted March 9, 1913. Patient semi-delirious. Condition reported to have started two weeks ago. Physical examination: Lower half of scrotum gangrenous and sloughing; on palpation emphysematous crackling detected above the gangrenous area; inflammation extends onto the shaft of the penis and the lower 2 inches of the abdominal wall. Catheterized with ease, no stricture, 1 ounce of cloudy urine obtained. Temperature sub-normal, Respirations 48. Heart action irregular. Patient died in profound toxemia thirty hours after admission.

Case 11. J. K. (A.4724½). Age forty-five. White. Laborer. Admitted April 24, 1911. Patient entered the hospital with a urethral discharge of two weeks' duration and the history that five days before admission scrotal swelling began, likewise a swelling of the left knee. April 26, scrotum swollen to three times its normal size, is excessively painful with gangrene starting in the dependant portion. Scrotum incised in several places disclosing gangrenous, subcutaneous tissue and liberating a quantity of stinking fluid. Eight hours later inflammatory condition had extended on to the lower abdominal wall which was crepitant on palpation. Further incisions were made in the inflamed portions of the skin of the abdomen, the underlying tissue being found completely gangrenous to the muscle layer, and masses of subcuticular tissue came away in stringy sloughs. Gas of repulsive odor escaped from every incision. Temperature 102.4°, later rising to 104° and falling gradually to subnormal. Patient remained profoundly septic and died on May 6, 1911. Culture showed the Bacillus aerogenes capsulatus.

Case 12. J. G. (A.3290). Age twenty-five. Colored. Porter. Admitted June 17, 1909. Patient a well developed Jamaican negro. Admitted in a stuporous condition. Denies venereal disease and gives an indefinite history of receiving a blow from a falling trunk. Physical examination: Scrotum found to be greatly swollen, very tender, and emitting an offensive odor (duration unknown). Skin of scrotum pre-

senting signs of approaching gangrene. Temperature 104°. Slough separated the day following admission, temperature reached normal on the eighth day. Testicles were completely exposed. Plastic operation done on July 7, 1909. Discharged, healed and cured, August 17, 1909.

Case 13. D. A. (A.1373). Age thirty-two. White. Mechanic. Admitted January 7, 1907. One week prior to admission had a dorsal slit operation done for chancroidal sores. Ten hours later penis started to swell and the tumefaction rapidly spread over both penis and scrotum. January 14, entire skin of both penis and scrotum has sloughed off, both testicles lie exposed. January 16, wounds granulating. February 6 and 20, small skin grafts transplanted from the right thigh with success. February 27, 1907, patient discharged, cured.

Case 14. J. L. (A.1484). Age forty-nine. Colored. Laborer. Admitted February 27, 1907. Two days ago "caught cold in privates" and his scrotum and penis began to swell. Condition not painful at first, and no history of any injury. Swelling continued the following day when scrotal wall became raw and oozing. Onset when patient was not working and "just lying quiet at home." Physical examination: Penis and scrotum enormously swollen, the latter tense, elastic, regular, bilaterally equal, heavy and with pseudo-fluctuation. On the under surface of the scrotum is an abrasion, oozing serous exudate. Highest temperature day following admission of 103.8°, with a pulse of 118. March 3, entire scrotum became necrotic and sloughed off en masse for a distance up to near the abdominal attachment. Testicles exposed and uninvolved. March 20, wound clean and granulating. May 5, 1907, patient discharged. Scrotum completely regenerated.

Case 15. E. S. (A.205). Age sixty. White. Driver. Admitted January 13, 1904. Patient had been undergoing a treatment for hemorrhoids. Two days before admission had felt pain in scrotum and the following day while lying down felt a sudden distention of the scrotum. Feels very little pain at present. Physical examination: Scrotum double normal in size, dull on percussion, fluctuation (?) present. Under portion of scrotum is black and gangrenous. Ischio-rectal region on left side indurated, red and swollen. Marked hemorrhoidal condition present. Temperature 100.8°. Entire scrotum sloughed off exposing testicles. Granulation began promptly, scrotum completely regenerated covering the testes as in the normal. Discharged April 4, 1904, cured.

Case 16. I. K. (A.180). Age twenty-five. Colored. Waiter. Admitted February 3, 1904. Eleven days before admission a sudden swelling of the scrotum to the size of a cocoanut took place. Became black and gangrenous. No preceding illness, no urinary difficulty. Physical examination: Whole lower half of scrotum found to have sloughed off, testicles are exposed in their tunicae, and are already covered with healthy granulations. March 8, 1904, edges of scrotum drawn together with silk sutures. March 24, 1904, union complete, patient discharged, cured.

SYMPTOMS

Though well pictured in the case cited in the beginning of this paper, certain features as seen in the whole group of 16 cases herein reported should be accentuated. The three cardinal features of the period of onset, (1) the "explosion," as Fournier calls it, while in perfect health, "comme par un veritable coup de theatre," (2) the rapid evolution of mortification, (3) and the total absence of the usual causes of gangrene, make up the picture of this morbid process. Emery adds a fourth characteristic in "the mode of termination of the disease by a cure," which I can hardly agree with, for though any recovery would seem remarkable at the onset, the condition nevertheless carries with it a high mortality rate. Whiting and Coenen each report death in 22 per cent of their collected cases. In my series of 16 cases 5 ended fatally, a mortality of 31.2 per cent. These deaths seemed to be from a profound toxemia as in two patients the local condition had completely responded to treatment, the slough separating cleanly and active granulation was progressing. Of the other three lethal cases, one died thirty hours after admission on the fifteenth day of his attack, one on the seventeenth day having entered the hospital but three days before, and one on the fifth day after admission and the seventeenth of his disease.

In six of the patients a penile swelling and gangrene preceded (in 2) or accompanied (in 4) the scrotal lesion. This I feel is but a concomitant lesion, the soft penile tissues sharing with the scrotum the virulent attack.

In all our cases at the Philadelphia General Hospital the gangrene has involved only the structures of the skin and subcutaneous tissues. In the scrotum this comprises all the tissues down to the tunica vaginalis testis, as likewise all the coverings of the cord to its true sheath. Only once has the tunica vaginalis been perforated in this series. When the penis is involved in the process all tissues down to the sheath of the corpora come away. In the cases where the abdominal wall has suffered invasion the tougher skin appears to retain its vitality while the subcutaneous fascia, the fat, and areolar tissues are found to be gangrenous to, but not involving, the deep fascia immediately covering the musculature. I have never seen record of a case where the gangrenous process in any way invaded the tissues of the thigh.

The rapidity with which the gangrene develops has been startling as compared with similar processes seen elsewhere about the body, or from different causes. In fourteen cases where the time is computable from their histories the average is eight days from onset to complete gangrene, though intimate analysis shows that the majority developed in a shorter period than this.[2] There is no relation between the rapidity of the process and a fatal outcome in this series.

It is usual that with the formation of the line of demarcation, and the separation of the slough, that the temperature and systemic symptoms show a tendency to return to normal, from which time convalescence is afebrile and uninterrupted.

ETIOLOGY AND PATHOLOGY

The greatest interest surrounds the etiology and pathology of the condition, and because I have so little to add to this phase of the subject myself, I wish to take advantage of my present opportunity, to elicit from my audience as full a discussion as possible from their experiences, that the cause and course of the disease may be the better delineated.

[2] Days that gangrene developed case by case: 1 on the second day; 1 on the third day; 2 on the fifth day and 2 on the sixth day; 3 on the seventh day; 1 on the eighth and 1 on the eleventh day; 2 on the fourteenth day; and 1 on the twenty-eighth day.

1. The lesion is undoubtedly infectious. There can be no question on this score.

2. Judging from the course of the disease; the mode of onset; the progressive spread in a typical case; the tissues involved; the limitations to which it proceeds and there stops; and the rarity of the involvement of the deeper structures, I accept the theory found in the French literature that pathologically it is essentially a lymphangitis.

3. There appear to be two types of infection, one producing aerosis and the other not. In 7 of my 16 cases emphysematous crepitation in the tissues was felt, and in several of these the escape of gas was audible on incision. One of them gave on culture the B. aerogenes capsulatus. In the non-gas producing cases the most frequent infecting organism is a streptococcus.

One finds great diversity of opinion as to the infecting organism reported in the cases in the literature. Bisset, Wendel, and Emery report a streptococcus infection; Dieulafoy an aerobic diplococcus, a facultative anaerobe, and an aerobic bacillus (B. aerobicus septicus); Pendi a pseudo-diphtheria bacillus; Thiry and Benech a fusiform spirillum (Vincent's), also a Klebs-Loffler bacillus; Spillman, and Thibault and Schulmann believe it an anaerobic infection, the latter finding the B. perfringens (B. aerogenes capsulatus).

It is regrettable that many of my patients got to the wards so late that bacteriological study was unproductive. In four of the patients the slough had already separated in part or in toto. In all cases one should be prepared to take anaerobic cultures and much may be expected from such a routine procedure as undoubtedly some of our failures were due to neglect of this form of study, and it should hold great promise in the future.

4. Six cases had local neighboring lesions that may have acted as portals of entry for the virulent organism. One had a phimosis, two had recent chancroidal infection (in one of whom a dorsal slit operation had been performed), one had a urethritis of nine days' duration and in his case the B. aerogenes capsulatus was isolated, one gave a very indefinite history of trauma, and the sixth was undergoing some treatment for hemorrhoids. In

the remainder the lesion appeared, as depicted, striking those enjoying their usual good health.

5. In the cases herein reported there is a marked predominance of onset in the winter months, no case being admitted during the months of May, July, August, or September. In October there was 1 admitted, 2 in November, 1 in December, 4 in January, 3 in February, 1 in March, 3 in April, and 1 in June.[3]

6. In passing it is of interest to find Allen comparing the condition to Noma, to which in truth it bears a close similarity.

7. The ages of these patients vary from twenty-four to sixty years, there being 3 in the third decade, 3 in the fourth decade, 5 in the fifth decade, and 5 in the sixth decade, showing a decided predominance for those past middle life.[4]

8. Ten were white men and six were colored. All types of labor were represented, both indoor and outdoor.

TREATMENT

Judging from the older literature it would seem that the massive sloughing of the scrotal walls in these cases precluded, in the minds of the physicians of the elder day, any chance of a regeneration, and apparently complete castration was generally advised and performed. "Indeed," says Allen, "this practice seemed at one time so prevalent that a physician near Boston entitled his report, 'Gangrene of the scrotum in which the testicles were not removed.'" Bisset in 1904 remarks regarding the regeneration of the scrotum in his patient "a termination practically unknown in such a case."

The question of the propriety of incising the inflamed scrotum is an open one. In the majority of cases, and especially in those limited to the scrotum alone, the process is so rapid and the gangrene appears so early that it does not seem that incision has made any difference in the result. The soft skin of the scrotal

[3] This was a case in a Jamaican negro taken ill after two months' sojourn in Philadelphia.

[4] The actual ages are as follows: 24, 25, 25, 32, 39, 39, 44, 44, 45, 49, 49, 50, 57, 58, 60, and 60 years, respectively.

wall does not withstand for long the tense swelling and the infection, and it is the rule that within eight days (frequently less), necrosis takes place.

In cases wherein the infectious process appears overwhelming, wherein the groins or the abdominal wall has become involved, or the patient shows evidence of profound sepsis, early incision and drainage is unquestionably indicated.

We have handled these patients in the following manner. The scrotum (and penis when involved) is incased in a copious dressing of gauze saturated with a solution of permanganate of potash 1 to 3000. When incision is performed, the wounds must be made long and deep, with through and through drainage of gauze. The wounds are irrigated with permanganate of potassium solution and the drainage gauze saturated therewith. In all cases at least daily dressing is performed with the renewal of the gauze drainage and copious irrigation, while in especially foul cases dressing is done twice daily. The external dressing is kept continually saturated with the permanganate solution.

When the slough is ready to separate as much as possible is removed at each dressing, and it is not unusual to have almost the entire mass lift off in one piece. It is at this stage that sharp secondary hemorrhages have been repeatedly encountered.

Once the wound is clean and granulation has commenced, it is our practice to dress it daily in one special way and to this, I believe, is accountable the excellent results that have been obtained in the formation of a new scrotum. After each routine cleansing and irrigation the saturated gauze is packed lightly up under the skin edge all around the fringe of scrotal tabs. The testicles are supported and pressed up against the perineum by a special bandage (Crossed Bandage of the Perineum). The first healing is a granulation between the two testicular coverings which rapidly adhere the one to the other and soon form a single pear-shaped mass. With each dressing the skin seems to creep down over the gauze under-packing, pushing it ahead of it as it granulates to the testicular surfaces. In most cases there really appears to be less of an actual proliferation of the scrotum, than an apparent voluntary stretching of the remnant tissue, and if properly

dressed, as above outlined, in due time a new scrotum forms, having the normal elasticity, and being freely movable on the underlying and encasing tissues of the testicles. Skin grafts may speed the process, not improve upon it: prepucial tissue is the choice when obtainable. Healing on the shaft of the penis has not been so promising in our cases, and a greater amount of scar tissue formation is apt to be the result, though leaving in every case a functionally satisfactory organ.

The result obtained in the patient whose history was the introduction to this paper was most satisfactory. On January 12, the scrotal slough separated and by the following day the wound was completely clean of all gangrenous tissue. Twice during these twenty-four hours the male nurse clamped and ligated actively bleeding vessels. The lesion on the shaft of the penis denuded a spiral strip of tissue 3 cm. broad extending from the dorsum at the corona to the peno-scrotal junction. Under careful dressing the scrotum was coaxed to encase the testicular mass and in seven weeks time a new scrotum had completely formed, with only an area 3 by 3 cm. in size remaining to be covered by epithelial proliferation. The patient being a negro it was easy to distinguish new tissue from old, and certainly four-fifths of the regenerated scrotum was original scrotal tissue stretched to cover in the defect. The final result left the patient with a scrotum no different in size from what might have been normal when in its contracted state from cold. The shaft of the penis showed heavier scarring and greater epithelization was necessary, though here too nature, slightly aided, perfected the final result, in that the previous phymotic prepuce semi-automatically retracted itself down over the shaft, leaving the glans exposed and granulating as a skin graft over part of the denuded area.

REFERENCES

(1) Allen: Jour. Cut. & G.-U. Diseases, 1894, xii, 55.
(2) Bisset: Lancet, January 25, 1904, i, 1793.
(3) Bok: Niderl. Tijdschr. v. Genesk., 1919, i, 519.
(4) Coenen and Przedborski: Beitrage z. klin. Chir., 1911, lxxv, 1 and 2 Heft.

(5) Dieulafoy: Quoted by Thibault and Schulmann.
(6) Emery: Archiv. gen. de Med., 1896, clxxviii, 407.
(7) Fournier: Semaine Medicale, 1883–1884.
(8) Kyle: Berl. klin. Wchnschr., January 8, 1917, liv, 27.
(9) Lequeu: Rev. gen. de Chir. et de Ther., 1918, xxxii, 504.
(10) Pendi: Quoted by Thibault and Schulmann.
(11) Spillman: Quoted by Thibault and Schulmann.
(12) Thibault and Schulmann: Bull. et Mem. de la Soc. Med. d. Hop. de Paris, January 31, 1919, 3 s., xliii, 70.
(13) Thiry and Benech: Quoted by Thibault and Schulmann.
(14) Wendel: Muench. med. Wchnschr., 1907, liv, 101.
(15) Whiting: Annals of Surgery, June, 1905, xli, 841.
(16) Zehr: Urol. and Cut. Review, 1914, xviii, 406.

SPINAL ANESTHESIA IN UROLOGY

GEORGE GILBERT SMITH[1]

Boston, Massachusetts

My only excuse for presenting this paper, which contains nothing really new, is the belief prevalent with many urologists that spinal anesthesia is a method to be avoided. There can be but two real objections to this method, aside from the fact that the operator may not be familiar with the technique.

The first objection one hears is that lumbar anesthesia does not always anesthetize; the second is that the method is attended or followed by consequences dangerous to the patient. In answer to the first objection, I must admit that occasionally, perhaps once in every ten cases, complete anesthesia is not obtained. In most of these failures, however, a very considerable degree of anesthesia is secured and by giving the patient enough gas or ether to dim his consciousness a satisfactory anesthesia is developed.

The second objection deserves a more detailed consideration. What possibly harmful results to the patient may be caused by spinal anesthesia? In reading the literature on lumbar anesthesia written between 1900 and 1915, I found mention of various nerve disturbances such as ocular palsy caused by this method. In later literature and in my own experience, I have never seen or heard of a case in which anything more than the most transitory nerve disturbance followed spinal anesthesia. Headaches do occur and may be severe but always disappear inside of two weeks. As a matter of fact, I have not encountered any of these in recent cases. Immediate fatalities from spinal anesthesia have occurred although so far I have been fortunate enough not to have seen any. I cannot believe that the intradural injection of novocain if properly performed can have such serious results.

[1] Read at a meeting of the American Urological Association, March 24, 1920.

Death must be due to one of three causes: (1) absorption into the circulation of a toxic drug; (2) paralysis of the respiratory center; (3) vasomotor collapse. It has been a rule with me not to inject more than 2 cc. of a 5 per cent solution of novocain. That contains 0.1 gram of the drug. In using novocain as a local anesthetic one frequently injects as much as 0.6 gram which is six times the amount used in spinal anesthesia. The interchange of substances between the blood and spinal fluid is known to be slow. It would seem therefore that there cannot be sufficient absorption from the spinal canal to cause general toxemia, and that the use of the vague term "toxic effect" when applied to the phenomena following spinal anesthesia should be discontinued.

Paralysis of the respiratory center by a small quantity (2 cc.) of novocain solution injected into the lumbar region is equally unlikely. The solution would become so diluted by the time it had diffused upwards through 35 cm. of spinal fluid that it could not possibly exert a paralyzing effect upon the bulbar centers or even upon the phrenic roots, which leave the cord at the level of the fifth cervical segment. Smith and Porter have shown that the injection of novocain even into the dorsal region of the canal will not cause respiratory paralysis unless the injection needle is directed towards the head of the animal. It has occasionally happened that respiratory paralysis has followed spinal anesthesia. This paralysis, however, in the two cases in which I have observed it, has lasted only a few minutes. It was due, I believe, not to the direct effect of the drug upon the respiratory centers (in which case the paralysis would have been more lasting) but to the anemia of those centers brought about by the extremely low blood pressure.

This brings us to the third possible cause of death. Vasomotor collapse is a real danger. It is seldom fatal but gives rise to a number of distressing symptoms. The patient complains of a feeling of faintness and of nausea, he becomes pallid and perspires; the respiration becomes slow with an occasional deep sigh, the pulse rate does not increase but the character of the pulse changes and becomes thready and weak. Frequent read-

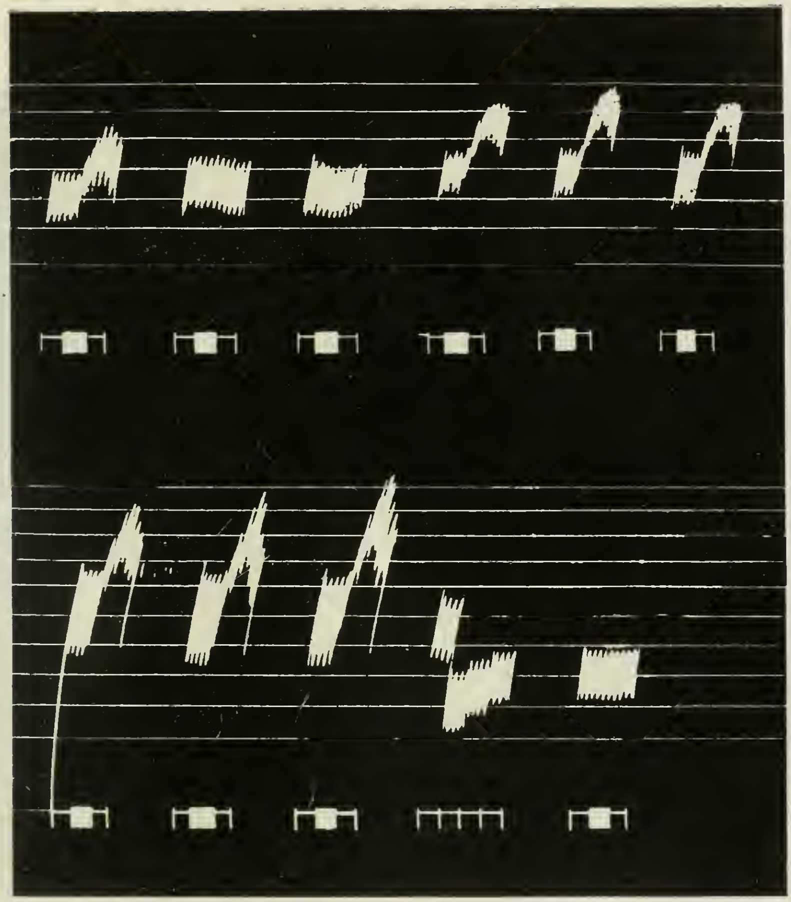


FIG. 1. The original size. Injection of 0.01 gram novocain and adrenalin in dilute solution (1 cc.) at lumbar VII causes paralysis of dorsal columns extending to dorsal XI, and perhaps above. Brachial rise reduced from 65 to 33 per cent.

Lower curve—left to right

1. Sciatic stimulation 12.10 p.m.
2. Brachial stimulation 11.14
3. Lumbar VII stimulation 12.15
4. Record of blood pressure 12.17; (12.22 Injection of drug); 12.25; 12.28; 12.31
5. Sciatic stimulation 12.32

Upper curve—left to right

1. Brachial stimulation 12.35 p.m.
2. Lumbar VII stimulation 12.37
3. Dorsal XI stimulation 12.39
4. Sciatic stimulation 3.25
5. Lumbar VII stimulation 3.27
6. Dorsal XI stimulation 3.29

Scale: 50, 70, 90, 110, 130, 150, mm. Hg.

Experiment 45, curarized cat. February 26, 1915.

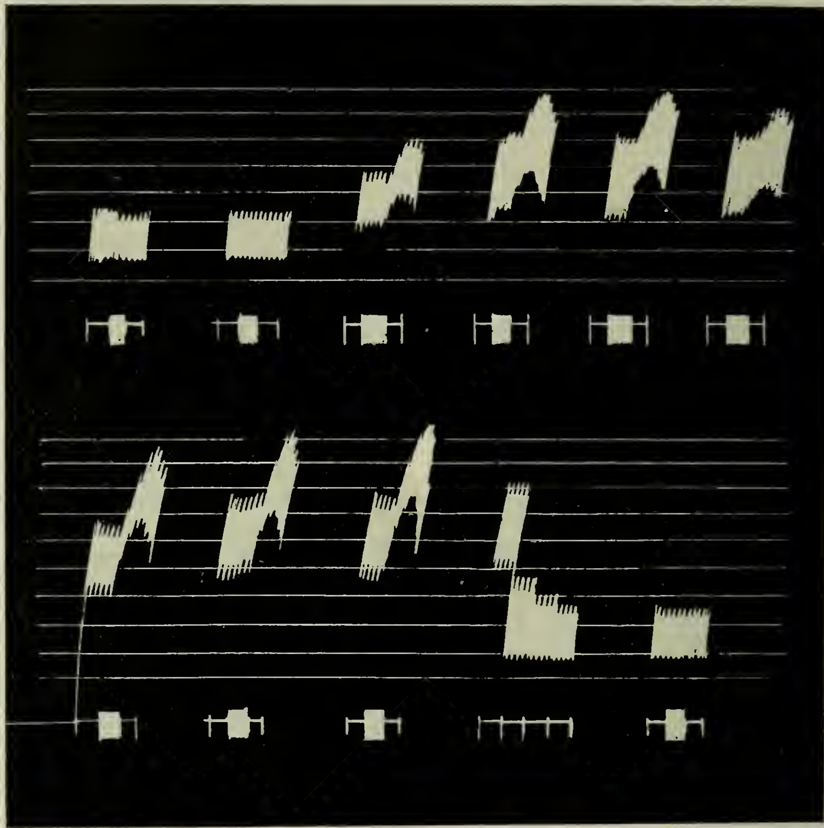


Fig. 2. The original size. Injection of 0.01 gram novocaine and adrenalin (0.2 cc.) at Dorsal VI causes fall in blood pressure from 110 mm. to 45 mm. in three minutes with abolition of vasomotor reflex from sciatic and brachial.

Lower curve—left to right

1. Sciatic stimulation 8.55 p.m.
2. Brachial stimulation 8.58
3. Dorsal VI stimulation 9.01
4. Record of blood pressure 9.02 (9.03 Injection of drug) 9.06 9.09 9.12
5. Sciatic stimulation 9.13

Upper curve—left to right

1. Brachial stimulation 9.15 p.m.
2. Dorsal VI stimulation 9.17
3. Brachial stimulation 9.42
4. Brachial stimulation 10.12
5. Sciatic stimulation 10.14
6. Dorsal VI stimulation 10.15

Scale: 30, 50, 70, 90, 110, 130, 150, mm. Hg.

Experiment 43, curarized cat. February 19, 1915.

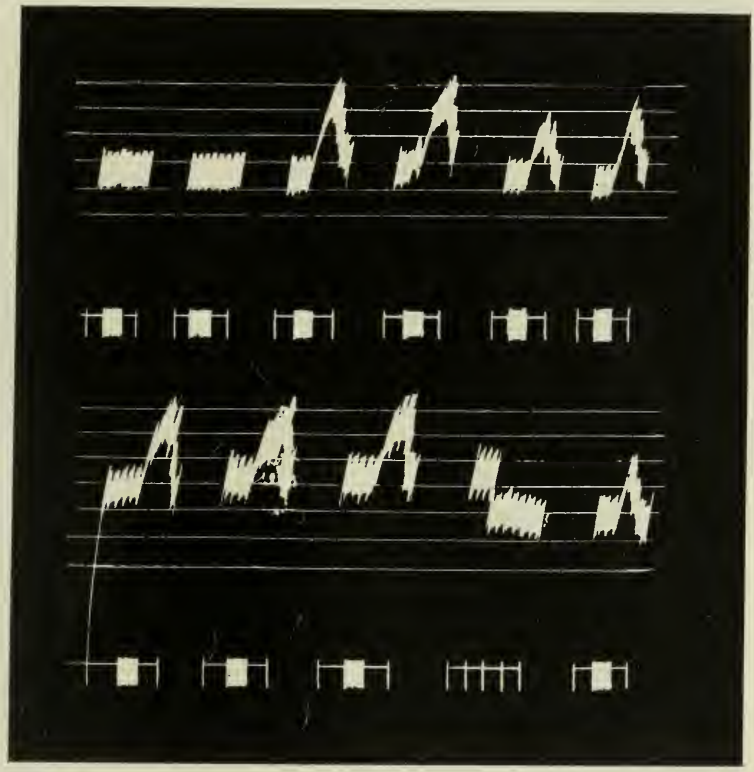


FIG. 3. The original size. Injection of 0.01 gram novocaine and adrenalin (0.2 cc.) at Lumbar VII causes fall of blood pressure from 120 mm. to 95 mm. in three minutes. Paralysis of sciatic incomplete eleven minutes after injection. Elevation of foot of board at angle of 30°, eighteen minutes after injection, is followed by complete paralysis of sciatic nerve.

Lower curve—left to right

1. Sciatic stimulation	9.11 p.m.
2. Brachial stimulation	9.13
3. Lumbar VII stimulation	9.15
4. Record of blood pressure	9.17 (9.22 Injection of drug) 9.25 9.28 9.31
5. Sciatic stimulation	9.33

Upper curve—left to right

1. Sciatic stimulation	9.48 p.m.
2. Lumbar VII stimulation	9.49
3. Lumbar I stimulation	9.51
4. Brachial stimulation	9.54
5. Sciatic stimulation	10.22

Scale: 70, 90, 110, 130, 150, 170, 190, mm. Hg.

Experiment 42, curarized cat. February 16, 1915.

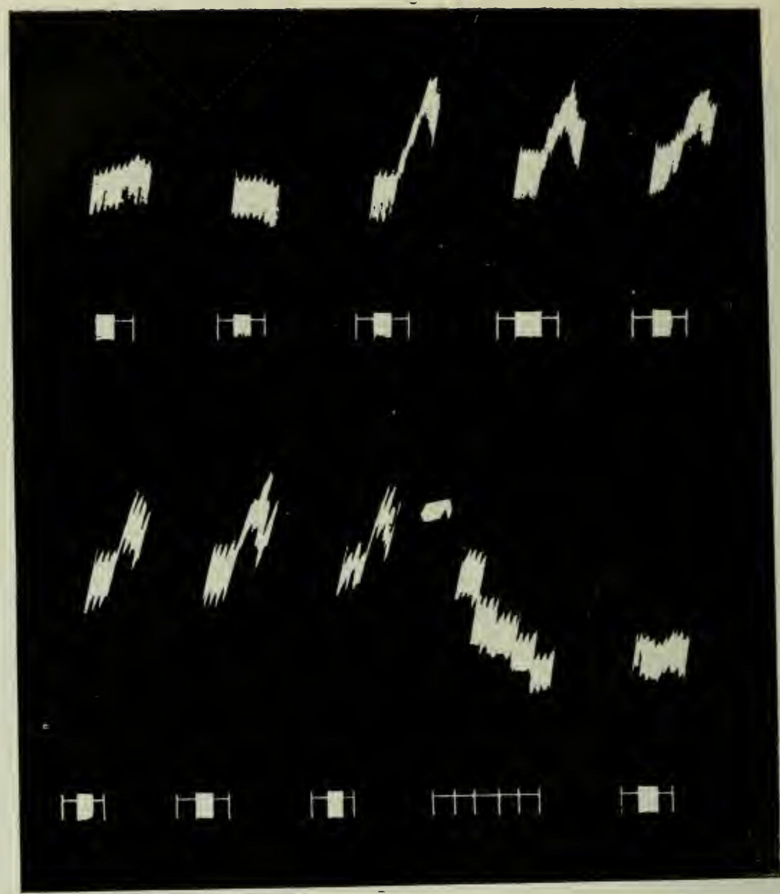


FIG. 4. The original size. Injection of 0.01 gram novocain and adrenalin (0.2 cc.) at cervical II cephalad causes fall of blood pressure which is gradual rather than abrupt, due probably to slower action of drug on cord itself than on thoracic roots. Dorsal columns blocked, but vasomotor mechanism below D I is unaffected.

Lower curve—left to right

1.	Sciatic stimulation	9.40 p.m.
2.	Brachial stimulation	9.43
3.	Cervical II stimulation	9.46
4.	Record of blood pressure	9.48 (9.49 Injection of drug) 9.52 9.55 9.58 10.01
5.	Sciatic stimulation	10.03

Upper curve—left to right

1.	Brachial stimulation	10.05 p.m.
2.	Cervical II stimulation	10.07
3.	Dorsal II lateral surface stimulation	10.42
4.	Sciatic stimulation	11.40
5.	Brachial stimulation	11.43

Experiment 46, curarized cat. March 4, 1915.

ings of the blood pressure during the course of spinal anesthesia have shown that these symptoms occur simultaneously with a fall in the blood pressure. I have seen the systolic pressure drop in the space of five minutes from 155 to a point so low that the Tycos sphygmomanometer would no longer register that pressure. It was without any question below 50 mm. Hg.

Although the vasomotor collapse occasioned by spinal anesthesia lasts as a rule for only fifteen or twenty minutes, its manifestations are sufficiently alarming and its effect upon weakened heart muscle sufficiently undesirable to constitute a serious objection to the method of anesthesia which brings about such a collapse. With the idea of learning how to eliminate this undesirable feature, I took the problem to Dr. William T. Porter, Professor of Comparative Physiology at the Harvard Medical School, and we together endeavored to work it out experimentally upon the cat. The detailed account of our experiments, which was published in the American Journal of Physiology for July, 1915, is too long to repeat here. In brief, we performed seventy-two experiments upon fifty cats. In all cases laminectomy was done and the dura exposed, so that we could be certain that the injection was made correctly. The solutions used were made from tablets "C," containing novocain and adrenalin, tablets "D," containing novocain and sodium chloride, and the ready made solutions of tropacocain which we formerly employed for spinal anesthesia. Figures 1 to 4 are records of four typical experiments.

In general it may be said that these experiments bore out the theory that the fall in blood pressure during spinal anesthesia is due neither to toxicity of the drug nor to paralysis of the vasomotor center but to paralysis of the vasomotor fibers regulating the tone of the blood vessels in the splanchnic area. The most important of these fibers are given off from the spinal cord from the second to the seventh dorsal segment; some of lesser importance are given off as far down as the first lumbar. Other conclusions reached from our experiments were these:

Regarding the diffusion of the drug, the bulk seemed on the whole a factor of greater importance than the strength of the solution. Dilute

solutions usually but not always spread farther than concentrated solutions.

Fixation of the drug is only partial. In three experiments after 25, 18, and 16 minutes respectively, enough remained free to paralyze other nerve fibers.

Gravity is a factor of some importance; tilting the animal at an angle of 40 degrees, head downward, increased the diffusion of the drug.

The specific gravity of spinal fluid is estimated at from 1.003 to 1.007 (Barker, British Medical Journal, vol. 1, pp. 665, 1907). The specific gravity of a 5 per cent solution of novocain such as we use has been estimated by Dr. Denis, physiological chemist at the Massachusetts General Hospital, to be 1.007. There is, therefore, no great difference in the specific gravity of the two fluids.

With the above data as a basis a method of giving spinal anesthesia which gives much less vasomotor collapse than was formerly seen has been worked out by Freeman Allen, anesthetist at the Massachusetts General Hospital, and myself.

The chief practical points to bear in mind are these; diffusion of the drug toward the head to a height sufficient to paralyze the nerve roots between the second and seventh dorsal vertebrae will cause profound vasomotor collapse. To avoid this upward diffusion the quantity of fluid injected should be small (2 cc.) and the injection should be made with as little force as possible. Placing the patient in Trendelenburg position even fifteen or twenty minutes after the injection, will cause the drug to diffuse towards the head and will increase the height of the resulting paralysis.

Our method of procedure is as follows: the patient is given $\frac{1}{6}$ or $\frac{1}{4}$ grain morphia according to size, one-half hour before operation. The drug used for spinal anesthesia is tablet C, which contains 0.05 gram novocain and 0.000083 gram adrenalin, or the corresponding tablet of apothesine. Two tablets are dissolved in about 2.5 cc. distilled water and boiled down until the total amount equals 2 cc., thus making a 5 per cent solution. The drug may be injected with the patient lying upon the side. I

have done this a few times satisfactorily. Boyd and Yount, who have employed spinal anesthesia in 6229 cases, habitually employ this position (J. A. M. A., 1917, lxviii, 601–604).

Our custom, however, is to have the patient sit upon the operating table with his feet upon a chair. The hands should drop between the thighs, the chin should be brought as close to the sternum as possible (fig. 5). The back should be bowed as much as possible but not bent forward at the hips (see figs. 5 and 6). The back is scrubbed with soap and water and with alcohol; a towel is placed across the back at the level of the iliac crests. This line crosses the spine of the fourth lumbar vertebra; the injection is usually made between the second and third lumbar spines (fig. 6). A flexible lumbar puncture needle with an obturator is used. When the canal is entered the obturator is withdrawn and if the fluid flows freely about 1 cc. is allowed to escape. A 5 cc. Record syringe containing the 2 cc. of novocain is connected with the needle and from 1 to 2 cc. of spinal fluid is drawn into the syringe. The entire amount of fluid is then injected very slowly and the needle withdrawn. The patient is then placed upon his back with head and shoulders slightly elevated; his eyes are covered by a towel; the operative field is prepared; within five minutes usually, but certainly within ten minutes, anesthesia should be present, from the level of the umbilicus down. If it is not, the patient is placed in Trendelenburg position for about thirty seconds. This manoeuver will increase the height of the anesthetic zone very quickly. The operator then tests the sensitiveness of the skin by pricking it with tooth forceps; some patients keenly alive to the possibility of being hurt appear hypersensitive. With these, the administration of a few whiffs of ether or of gas will suffice to detract the attention and to allow the operation to proceed. In most cases of prostatectomy the patient has a feeling of pressure as the gland is being enucleated. If anesthesia does not occur within twenty minutes, the injection should be repeated. Anesthesia lasts for a period of one to one and one-half or rarely two hours; it is characterized by pronounced flaccidity of the abdominal muscles, a condition which is very helpful in prostatectomy or in opera-

tions in which retraction of the abdominal wall is needed. The patient breathes quietly and easily and unless the blood pressure has been greatly lowered by paralysis of the splanchnic roots, there is no vomiting. If vasomotor collapse does occur, re-

Fig. 5. Lateral View of Position Assumed by Patient Preparatory to Injection of Anesthetic

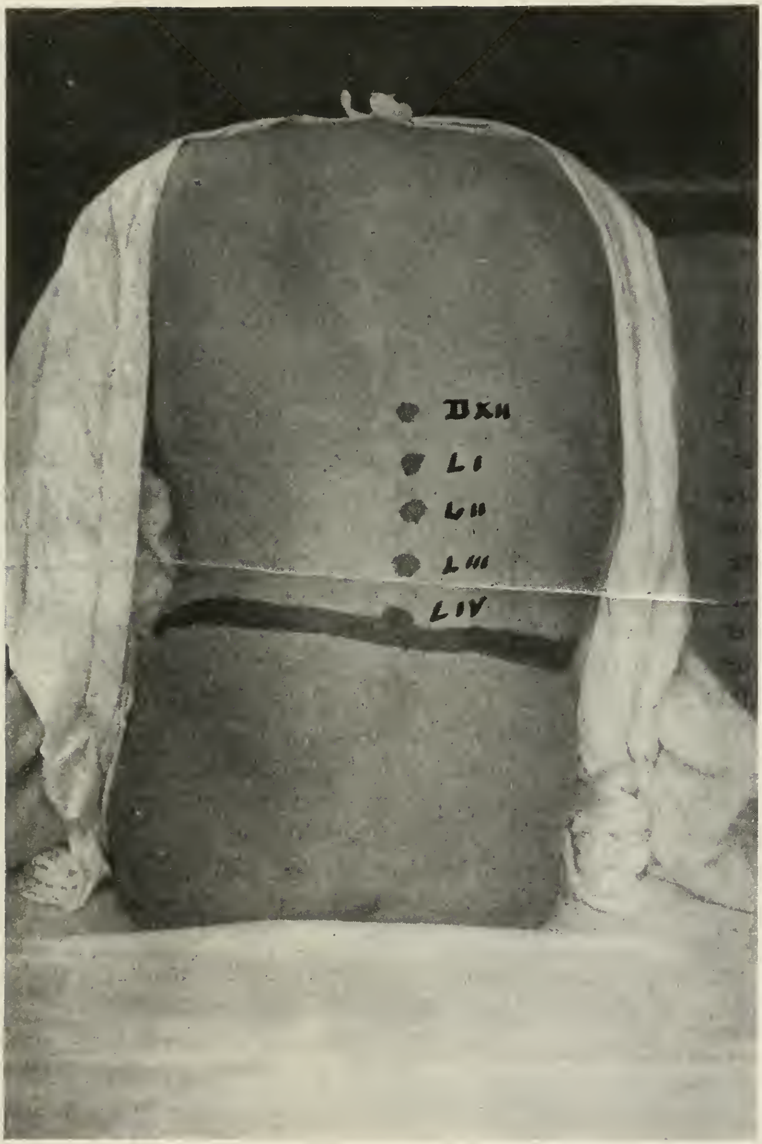


Fig. 6. Dorsal View of Position Assumed by Patient Preparatory to Injection of Anesthetic

breathing seems to be very efficient in stimulating respiration and thereby pumping the blood by means of increased negative intra-thoracic pressure, out of the large abdominal veins into the general circulation.

After the operation it is not unusual to have some nausea. This is due, I believe, to the shaking up which the patient gets as he is lifted from table to truck, from truck to bed. As soon as he is in bed he is given a cup of hot tea and shortly after is started on frequent sips of water. This ability to take water immediately after operation is an important advantage of spinal anesthesia.

This method of anesthesia, in our experience, is becoming more and more satisfactory. It is employed by Arthur Chute and myself in almost every prostatectomy. It is especially valuable in cases of retention due to stricture, in which ether would be a severe handicap to kidneys already badly damaged, and in cases of tuberculosis in which an irritable bladder would otherwise preclude protracted search for the ureters. When the latter are catheterized the kidneys are found to be secreting as well as if the patient were not anesthetized. Cystoscopy is much easier when spinal anesthesia is used than when the patient is under ether, as the respiration is not so stertorous, the bladder is entirely free of spasm and the cystoscopist feels that he has plenty of time. For most operations upon the external genitals local anesthesia can be employed if ether is contra-indicated. Spinal anesthesia should not be used when local anesthesia will suffice. For operations upon the lower urinary tract in patients with poor heart or kidneys, with diabetes or with any other condition in which ether narcosis is attended with risk, spinal anesthesia offers a most acceptable substitute.

The objections to spinal anesthesia vanish to a large extent with familiarity. Its advantages, especially in certain cases of the type with which genito-urinary surgeons are so well acquainted (I mean the cases with a combination of uremia and sepsis) are many. The technic requires only the ability to perform lumbar puncture and an adherence to the principles laid down in this paper.

A PROCEDURE FOR THE CURE OF PROSTATIC ABSCESSES[1]

A. RAYMOND STEVENS

Prompted by the feeling that convalescence from the operative procedures in vogue for prostatic abscess was unduly long, we became interested on the Urological Service at Bellevue Hospital, last summer, in trying out methods which offered possibilities of relief to the patient without a prolonged stay in the hospital. Since that time no open operations have been done for prostatic abscess except when this was found at first examination to be accompanied by the extracapsular infection known as perineal abscess.

We had previously tried various operations:

a. Drainage into the posterior urethra, (1) through a suprapubic intravesical approach, or (2) through a perineal incision opening into the membranous or the bulbous urethra.

b. Drainage into the rectum in selected cases.

c. Drainage into the perineal space through the posterior prostatic capsule, after a careful dissection between the prostate and the anterior rectal wall.

The suprapubic approach was employed in six or eight cases, but the time of healing averaged as long, if not longer, than the perineal sections. We were doubtful whether the perineal incision, per se, was a factor in producing later so-called sexual neurasthenia, as had been urged, but we were sure that a drained abdominal wound leaves a weakened abdominal wall. Hence this operation was discontinued.

Perineal drainage through a mid-line incision, opening the abscess into the posterior urethra by a finger introduced through a longitudinal cut in the bulbous urethra, has been the most com-

[1] Read at the meeting of the American Urological Association, New York, March, 1920.

mon operation employed at Bellevue Hospital until the past year. This has been unsatisfactory chiefly because of the prolonged convalescence, although relief of the symptoms demanding operation has been obtained. The cases have not been followed in detail and in numbers sufficient to show us whether this operation leads ultimately to an unduly large number of protracted cases of urinary infections, as has been maintained by some workers.

Incision of the rectal wall has been a remarkably and surprisingly efficient procedure in selected cases.

Drainage through the posterior capsule of the prostate, without opening the urethra, is an operation which has been done at Bellevue Hospital only occasionally. The writer himself was discouraged after one such operation he performed eight years ago. The immediate outcome was satisfactory, but the patient had been out of the hospital only about a week when he returned with a recurrent prostatic abscess which was then opened by the intra-urethral method. This is the only case he can recall which required a second operation when treated by any of the above mentioned methods.

The two procedures employed the past year are (1) aspiration through a needle plunged into the perineum, reported elsewhere by Barringer, and (2) opening of the abscess into the posterior urethra by a metal sound. The latter method is not presented as a new one, but because of the results obtained. Without going into the arguments pro and con for opening a prostatic abscess into the urethra or for opening it through the posterior capsule of the prostate into the perineal space, we feel that if one favors an opening into the posterior urethra, the "sound" method has distinct advantages over open operation.

The routine has been to clean the patient, place him in the lithotomy position, administer gas and oxygen anesthesia (one case was done under local anesthesia), and introduce a rather pointed sound with a small curve (F. 23) into the urethra. One finger in the rectum controls the rest of the procedure. The tip of the sound is located at the apex of the prostate, introduced about 2 cm. further, turned 90 degrees and with care forced through

the lateral wall of the urethra into the corresponding lateral lobe of the prostate. It is then withdrawn to the apex of the prostate and in similar manner made to enter the other lateral lobe. To be sure of a larger opening for drainage, a larger sound (F. 28) is put through the same manoeuvre. This, however, may be an unnecessary step. At this stage, slight pressure on the prostate produces, in most instances, a copious discharge of pus at the external urinary meatus. A simple irrigation fluid is then forced into the urethra, washing the urethral contents into the bladder. Finally a large rubber catheter is introduced and the bladder irrigated until clean. No catheter is left in the urethra.

Eight patients have been treated in this way. One man was fifty-two years old; the others ranged in age from twenty-three to thirty-four. Seven were admitted with recent gonorrhea, and one had had an old infection. Five were operated upon for retention of urine; none required post-operative catheterization, and all voided with ease on leaving the hospital (in two instances this was on the third day). One case had had retention, but did not require catheterization in the hospital; he was operated upon because of septic temperature which went above 104° prior to operation. The highest point the day after operation was 101°; the subsequent record showed no temperature above 99.2°. This patient also left the hospital on the third day following operation. Another case had no urinary symptoms but came to the hospital complaining of joint pains. Gross pus was obtained from his prostate at the time of operation. There were no untoward symptoms, and the patient declared his joints improved on discharge six days after operation. The last case in this summary had a large tender prostate, and had had painful and very frequent urination for two weeks. There was no residual urine when he was admitted to the hospital. The temperature ranged about 103° for twenty-four hours before operation; it was 104.6° the afternoon of operation but then steadily fell to 99° on the third day after operation, and remained there. The patient remained in the hospital a week, and was discharged with normal temperature and voiding easily and painlessly without frequency.

In all but one instance, gross pus was discharged at the urethral meatus after the "sound" operation. In no case was there more than trivial hemorrhage. Many of the patients had an initial rise of temperature the day after operation, as is commonly noted following the other operative procedures referred to. But the return to normal occurred earlier than when a perineal wound with its larger surface for absorption was added to the puncture of the urethral wall. In fifteen consecutive perineal sections for drainage of prostatic abscesses into the posterior urethra, performed during the year prior to our work (excluding one case which died, apparently from hemorrhage), the average time required after operation for the temperature to fall and remain below 100° was over four days. The average time in the cases here reported was about two and one-half days. The same group of patients with perineal sections remained in the hospital after operation, on an average, thirty-one days. The average stay in the hospital after the "sound" operation was six days.

One of our patients developed epididymitis after operation. Another had transient edema of the penis. No other complications occurred in hospital, or under observation afterwards. An effort was made to secure for urethroscopic examination the first five of the eight men treated, but none reported.

This brief report is offered in the belief that the method proposed gives as thorough relief from the symptoms demanding operation in prostatic abscess as do other procedures, and in as short a time. Moreover, convalescence has been easier and of much briefer duration than follows open operation. Although the field of operation is not open to view, the position of the operating sound is at all times determinable by the palpating finger in the rectum, and its movements are under good control.

CASE REPORTS (IN BRIEF)

These cases were all operated upon by the "sound" method, for abscess of the prostate. All were given gas and oxygen anesthesia excepting case VI, in which local anesthesia was used.

Case I. T. L., thirty-four years. Admitted May 6, 1919. Discharged May 23, 1919. Admitted during the fourth attack of gonorrhea, and with retention of urine which required regular catheterization to time of operation. Operation, May 9; much pus obtained. Temperature: 100.4° on day before operation; 103.5° the day after; gradually fell, but did not remain under 100° until the eighth day. No catheterization after operation.

Case II. P. B., thirty years. Admitted July 6, 1919. Discharged, August 31, 1919. Had had recent gonorrhea. Entered hospital because of arthritis. Examination: Prostate much enlarged and firm; seminal vesicles distended, not indurated. Operation, August 25; gross pus present. Temperature: normal before operation; rose to over 101° first two days after operation; 100° on third day; thence practically normal. Left hospital, joints better and walking fairly well.

Case III. C. D., fifty-two years. Admitted July 22, 1919. Discharged July 28, 1919. Had had recent gonorrhea. Urinary retention since July 19 and continuing to time of operation. Examination: Prostate, three times normal size and tender. Operation, July 25: thin pus obtained. Temperature: normal before operation; was 100.4° next day; normal on second day and subsequently. Had been catheterized regularly before operation; catheterization not required afterwards, but patient voided easily.

Case IV. L. D., thirty-four years. Admitted July 24, 1919. Discharged August 4, 1919. Had had gonorrhea several years before. Urinary retention since July 19; voided voluntarily, though frequently, in hospital. Ran septic temperature to 104°. Examination: Prostate and seminal vesicles formed a large, hard, irregular mass. Operation, August 1; no gross pus noted. On day after operation, temperature was 101°; subsequently, not over 99.2°. Urinary symptoms subsided. No catheterization required.

Case V. H. T., twenty-three years. Admitted October 4, 1919. Discharged October 14, 1919. Admitted during third attack of gonorrhea with retention for four days. This lasted to day of operation. Examination: Prostate much enlarged, hard and tender, projecting much into rectal lumen. Operation, October 7: Much pus obtained. Highest temperature before operation, 99.4°; 101.8°, first day after; was 100° next three days; then 99°. No catheterization needed after operation. Slight edema of penis was noted for few days after operation.

Case VI. J. D., twenty-four years. Admitted January 4, 1920. Discharged January 9, 1920. Had had old and recent gonorrhea. Ad-

mitted with history of painful and frequent urination of two weeks duration, and difficult defecation. Examination: No residual urine; prostate much enlarged, firm, tender, with possibly deep fluctuation. Operation, January 6; 4 per cent novocaine was slowly injected and held in urethra five minutes; no general anesthetic used; much pus obtained from left lobe of prostate; not sure that right lobe was opened. Procedure rather painful. Temperature: normal before operation; reached 99.5° first day after; thence under 99°. Patient left hospital on third day after operation, with acute symptoms subsided.

Case VII. J. F., twenty-eight years. Admitted February 16, 1920. Discharged February 24, 1920. Admitted with second attack of gonorrhea, complaining of sharp perineal pain and painful urination, with recent retention of urine. Examination: Prostate several times normal size; soft in mid-line, hard and irregular in both lobes. Left seminal vesicle normal; right seminal vesicle slightly indurated. Operation, February 17; much pus obtained. Temperature ranged about 103°, the twenty-four hours before operation; was 104.6°, afternoon of operation; 102° the next day; 100° on second day; subsequently not over 99°. No catheterization required after operation. Patient voided easily and painlessly on discharge.

Case VIII. P. C., twenty-two years. Admitted March 12, 1920. Discharged March 25, 1920. Admitted with recent gonorrhea (first attack), and history of retention of urine for three days. Had had suprapubic puncture. Examination: Prostate very large, indurated, rounded and bulging into rectal lumen. Both seminal vesicles distended and slightly indurated. Patient was catheterized occasionally in hospital; voided small amounts with great effort in the intervals. Residual urine over 600 cc. just before operation. Operation, March 19; much pus obtained. Temperature normal before operation; rose to 105.4° with sweats, first day after; 101.5° was reached on second and third days, below 100° on the fourth day, and normal thereafter. Catheterization on the fifth day showed no residual urine.

PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES OF THE PROSTATE GLAND

II. THE ACTION OF PROSTATIC EXTRACTS ON EXCISED GENITO-URINARY ORGANS

D. I. MACHT AND S. MATSUMOTO

From the Pharmacological Laboratory, Johns Hopkins University, and the James Buchanan Brady Urological Institute, Baltimore

INTRODUCTION

Our knowledge concerning the physiology of the prostate gland is still very incomplete, hence any experimental contribution to the subject should be of scientific interest. In the present investigation the authors have undertaken a study of the effects of prostatic extracts on the genito-urinary organs. It is well known that disturbances of bladder function are frequently associated with hypertrophy and other diseases of the prostate gland. It was therefore interesting to inquire into whether there is any relationship between the prostate gland, on the one hand, and the tonicity, as well as contractions, of the bladder, on the other. In order to make the study more comprehensive, however, the effect of prostatic extracts on all genito-urinary organs was investigated. The literature on the subject is very meagre as far as experimental data are concerned. The only references which the authors have been able to find are the work of Ott and Scott (1), who found that prostatic extracts stimulate the uterus; the experiments of Battez and Boulet (2), who noted a contraction of the bladder on intravenous injections of prostatic extracts; and a few observations by Dubois and Boulet (3), who also studied the action of prostatic extracts on the bladder, with no definite results.

METHOD

In the present research the effect of prostatic extracts on excised genito-urinary organs only was studied. The following organs were studied in this way: bladder, ureters, uterus, Fallopian tubes, vasa deferentia, and seminal vesicles. These organs were obtained from the following animals: the rat, guinea-pig, pig, rabbit, dog and cat. The method of study was the same as the one employed by the authors in their work on ovarian and corpus luteum extracts (4), and also extensively employed by the senior author in numerous papers published elsewhere. The freshly excised organs, or parts of organs, were suspended in a small glass chamber containing a nutritive physiological solution. One end of the preparation was fastened to a glass hook at the bottom of the chamber, while the other end was connected by means of a silk thread to the short arm of a lever, the long arm of which was adjusted so as to write on a kymograph. The long arm of the lever was about ten times as long as the short arm, so that the contractions recorded were magnified correspondingly. Through the small chamber containing the suspension preparation a constant stream of oxygen was kept bubbling, and the temperature of the physiological solution was kept constant at about 38°C. by immersing the small chamber in a jacket of water. The physiological solutions used were in some cases Locke's solution and in other cases Tyrode's solution. Inasmuch as Macht has shown that certain organs survive better in solutions of greater or lower hydrogen ion concentrations (5), the solution employed in case of the ureter and the bladder was generally Locke's solution, while Tyrode's solution was used in studying the other organs.

The prostatic extracts employed were obtained from the following sources: desiccated prostate of the ram (Armour's preparation), prostates of the dog, bull and steer, prepared especially by the authors, and extracts of normal and hypertrophic human prostatic tissue, obtained from the operating room of the Brady Institute. In most cases the extracts were prepared by macerating or rubbing the gland substance, fresh or desiccated, as the

case might be, with saline solution. In some cases, however, alcoholic extracts of the prostate were made and these evaporated and taken up in water when the experiments were to be performed. In case of all the aqueous extracts the strength of the solutions or suspensions was made to correspond to 10 per cent by weight of the fresh gland substance.

Experiments were performed by first suspending preparations in the warm and oxygenated physiological solutions and studying the curve of normal tonus and contractions. Then small doses of a prostatic extract were introduced directly into the chamber and their effect on the tonus and contractions was observed.

RESULTS

A summary of the results obtained is given succinctly in the subjoined table. In the table there will be noted the smallest effective dose or doses required to bring about a change in the tonus or contractions of any organ. The Arabic numerals indicate the quantity of the extract required to produce an effect. In all the experiments the original quantity of the physiological saline solution in the chamber was 25 cc. The Roman figures indicate the number of experiments performed in each case.

Figures 1 to 10 are shown as illustrations of the effects obtained.

A study of the table and of the illustrations will reveal the fact that all of the genito-urinary organs studied are stimulated by prostatic extracts but that the minimal dose required to produce such stimulation varies with the kind of organ, the animal from which it is obtained, and with the nature of the prostatic extract. A summary of all the numerous experiments performed by the authors shows that the organs most quickly or easily excited to contraction by prostatic extracts are the uterus and the tubes. Next in order come the bladder and the ureters, and lastly the vas deferens and the seminal vesicle.

Stimulation of the uterus by prostatic extract is not surprising as the authors have found that that organ can be induced to contract by the addition of almost every glandular extract. Of greater interest, however, is the behavior of the bladder on treat-

TABLE 1

	Bladder.					Ureter.	Uterus.					Fallopian Tube.		Vas Def.	Sem. Vesic.
	Rat.	Guinea Pig.	Pig.	Rabbit.	Cat.	Pig.	Rat.	Guinea Pig.	Pig.	Dog.	Cat.	Pig.	Cat.[x]	Rat.	Rat.
Prostate — Ram.	(2.5)-5.0-8.0	(0.5)-2.0	(0.5)-1.2-2.0	0.6-1.2-	0.5-1.0	4.0-8.0-10.0	0.5-1.0	0.25	0.25	0.5-1.0	(0.25)-0.5	(1.0)-3.0-7.0	0.5	(2.0)-5.0-7.0-	5.0-7.0-10.0
	XVII.	III.	V.	IV.	IV.	VI.	XVII.	VII.	XIII.	XI	XIV.	VI.	III.	XXIV.	XV.[xx]
" Dog.	5.0	2.0	2.5-	1.0	1.0	5.0-10.0	0.5	0.3		0.6	1.0	3.0	0.4	7.0-9.0-	5.0-9.0
	XII.	V.	III.	III.	IV.	III.	VII.	III.		III.	III.	III.	III.	VII.	III.
" Human, Normal.	5.0	1.5	2.5	1.0	1.5	5.0-10.0	0.5-1.0	0.25	0.5-1.0	0.7	0.5-1.0	2.5	0.5	7.0-10.0-	7.0-10.0
	XI. *	II.	III.	III.	IV.	III.	VI.	III.	III.	III.	XXIII.	III.	III.	V.	II.
Human, Hypertrophic	5.0	1.5	2.5	1.0	1.5	5.0-10.0	0.5-1.0	0.25		0.7	0.5-1.0	2.5	0.5	7.0-10.0-	7.0-10.0
	XI. *	II.	III.	III.	IV.	III.	VI.	III.		III.		III.	III.	V.	II.
" Bull.	5.0	0.25				7.0-10.0-	1.0	0.2				2.0		8.0-10.0-	10.0-
	IV.	V.				III.	VII.	IV.				IV.		IV.	IV.
" Steer.	5.0	0.25				7.0-10.0	1.0	0.2				2.0		8.0-10.0-	10.0-
	IV.	V.				III.	VII.	IV.				IV.		IV.	IV.

* In exceptional cases (2 out of 11 experiments) (in both normal and hypertrophic) a slight decrease of tonus was seen.

[x] Pregnant uterus of cat.

[xx] 15 experiments were made; in one preparation the dose was

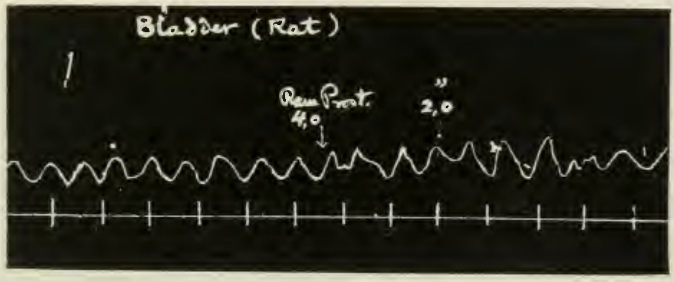


FIG. 1. BLADDER OF THE RAT

Showing effect of extract of ram's prostate on the tonus and contractions. A slight stimulation is seen after very large doses of the drug (4 to 6 cc.). Time markings in all figures are one minute intervals.

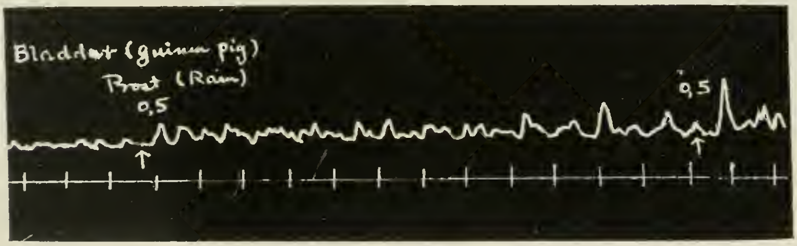


FIG. 2. BLADDER OF GUINEA-PIG

Showing action of prostatio extract from the desiccated gland of the ram

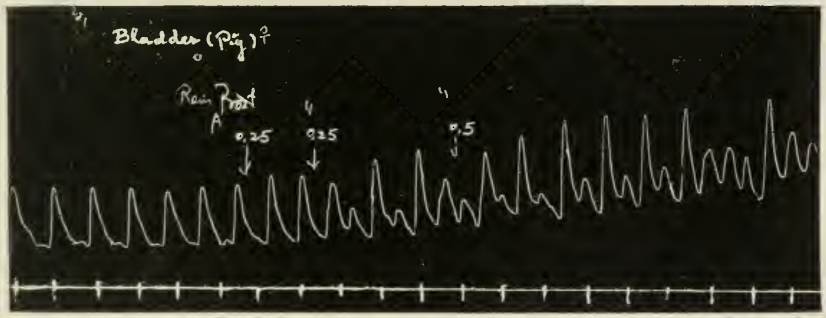


FIG. 3. BLADDER OF THE PIG

Effect of extract of the prostate of the ram on tonus and contractions

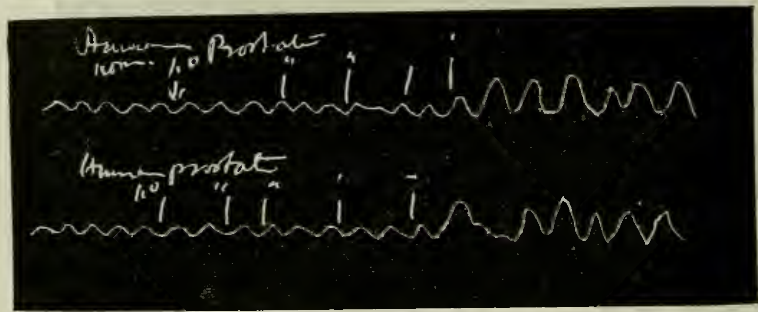


Fig. 4. Bladder of Rat

Showing effect of extract of normal human prostatic tissue

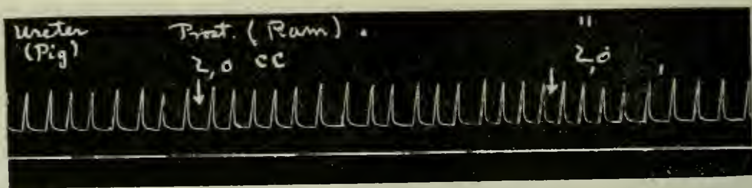


Fig. 5. Ureter of the Pig

Note how even large doses of prostatic extract (4 cc.) produce no effect

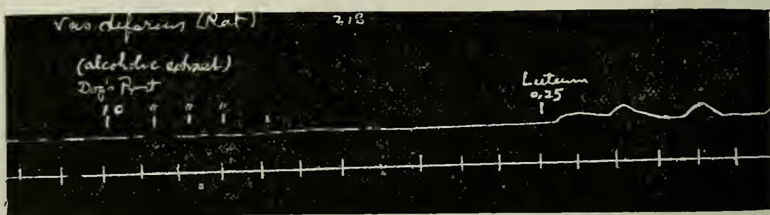


Fig. 6. Vas Deferens of the Rat

Showing the difference in action between the extracts of the prostate and the corpus luteum. A large dose of dog's prostate (5 cc. of alcoholic extract) produces no effect; while a very small dose of corpus luteum extract (0.25 cc.) stimulates the vas deferens to contraction.

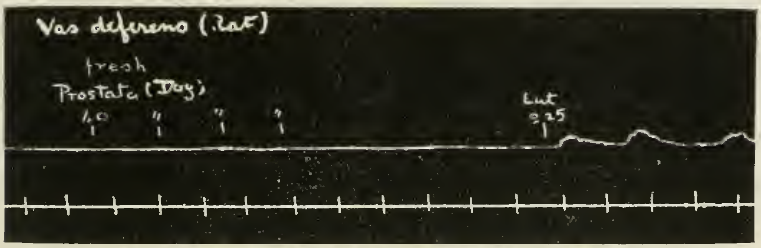


Fig. 7. Vas Deferens of the Rat

Similar to that in the preceding figure. Here a saline extract of a freshly excised prostate of the dog was used.

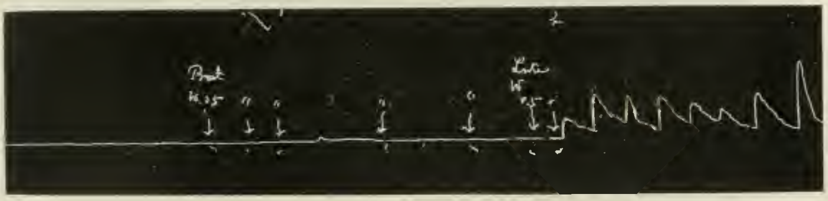


Fig. 8. Seminal Vesicle of the Rat

Showing effects of prostatic and corpus luteum extracts. Note that 2.5 cc. of prostatic extract (ram's) produced no effect, while 0.5 cc. of corpus luteum extract (sow) induces powerful contractions.

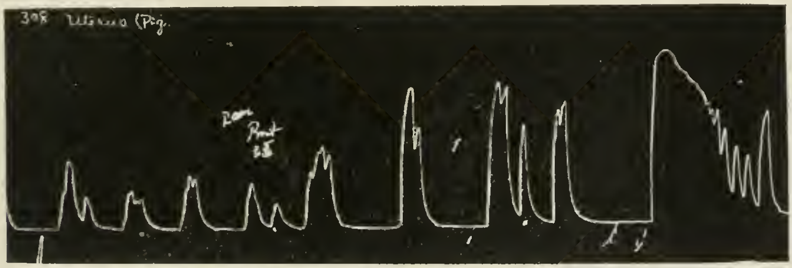


Fig. 9. Uterus of the Pig

Showing effect of a saline extract of ram's prostate, 0.5 cc. producing a stimulation.

ment with prostatic extracts. As a result of the present investigation it is evident that there is no definite or specific relationship between the tonus and the contractions of the bladder and extracts of the prostate gland. The idea, therefore, that some "internal secretion" or endocrine function of the prostate gland exerts an influence on the tonus or other functions of the bladder is certainly not substantiated by the present study.

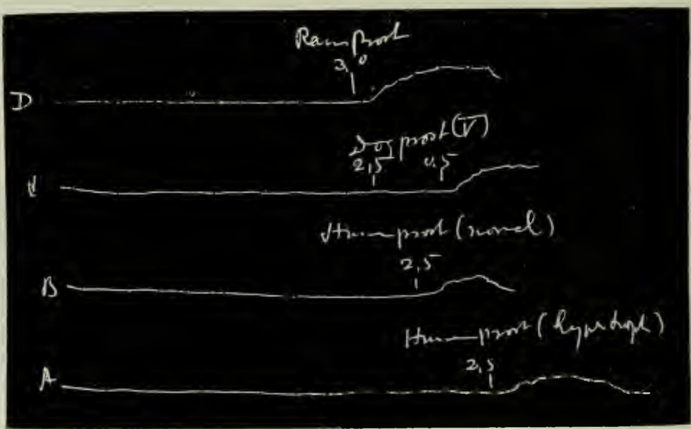


Fig. 10. Fallopian Tube of the Pig

Showing effect of prostatic extracts. *A*, human hypertrophied prostate; *B*, normal human prostate; *C*, prostate of the dog; *D*, prostate of the ram.

CONCLUSIONS

1. The effects of various prostatic extracts were studied on the excised genito-urinary organs of various animals.

2. It was found that prostatic extracts stimulate the tonus and contractions of all the organs, provided a sufficient quantity of the drug is used.

3. The order of sensitiveness of the various organs in this respect is as follows: uterus, Fallopian tubes, bladder, ureter, vas deferens, and seminal vesicles.

4. The data obtained in this investigation do not warrant the assumption of any specific relationship between prostatic secretion and the tonus or contractions of the bladder.

REFERENCES

(1) Ott and Scott: Jour. Exp. Med., 1909, xi, 326.
(2) Battez and Boulet: Compt. Rend. Soc. Biol., 1913, lxxiv, 8.
(3) Dubois and Boulet: Compt. Rend. Soc. Biol., 1912, lxxii, 701.
(4) Matsumoto and Macht: Jour. Urol., 1919, iii, 63.
(5) Macht: Jour. Urol., 1917, i, 97.

LOCAL TREATMENTS FOR SEMINAL VESICULITIS WITH A DESCRIPTION OF SOME NEW METHODS[1]

V. D. LESPINASSE

Chicago, Illinois

The treatment of seminal vesiculitis by injection through the vas deferens originated with Dr. Belfield. Since that time the only improvement on the original technic has been vaso puncture as advanced by Thomas. Knowing well the possibilities of this method of treatment, particularly in acute and sub-acute seminal vesiculitis, I have worked with it and wish to present to you today: first—some entirely new methods of manipulating the vas deferens so that medicaments can be injected through it into the seminal vesicles. Second—to show the results of some experimental work that prove that the choice of the medicaments injected into the vas deferens is a very important one and that no solution should be injected into the human vas deferens without preliminary experimentation.

The first technic I wish to present for your consideration has been named "the loop vas." In this technic the vas is exposed and freed for 2 to 3 inches, pulled up out of the wound and the wound sutured, leaving the vas projecting from the wound as a loop. Next a Thiersch skin graft is cut and wrapped around the exposed vas in the same manner as a base-ball bat is taped. A piece of thin rubber or oiled silk is now laid over the wound and another folded over the vas. When healed, the vas is covered with a thin layer of epithelium projecting free from the scrotum. The results from this technic were disappointing as the layer of epithelium developing was much thicker than expected and consequently I do not recommend this operation for general clinical use.

The second technic is "intra-dermal transplantation of the vas." The vas is freed for an inch, brought out of the wound

[1] Read at the meeting of the American Association of Genito Urinary Surgeons, Atlantic City, June, 1919.

Fig. 1. Schematic Drawing Showing the Loop Vas Operation Nearly Completed

The vas is drawn out of the scrotum, the scrotal wound sewed and the vas is being wrapped with the first Thiersch graft.

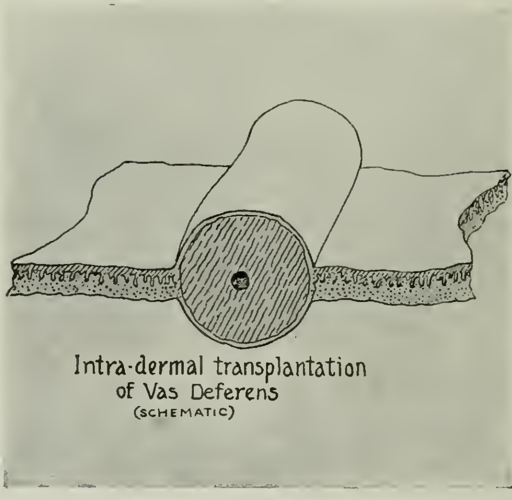
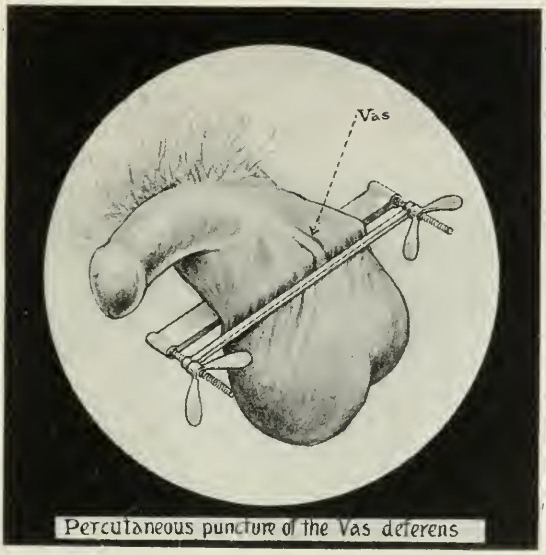


Fig. 2



Percutaneous puncture of the Vas deferens

Fig. 3. Shows the Big Clamp Applied to Scrotum and Turned so that the Vas Appears Beneath the Skin and is Held Steady

Percutaneous puncture of the Vas deferens

Fig. 4. Shows the Puncture Clamp in Place Beneath the Vas and Traction Made, Bringing the Vas Up Directly Beneath the Skin

which is now sutured, leaving the skin edges slightly apart. The vas is now allowed to settle down into the space between the cut edges of the skin. Its center should be level with the skin surface. A thin layer of epithelium grows over

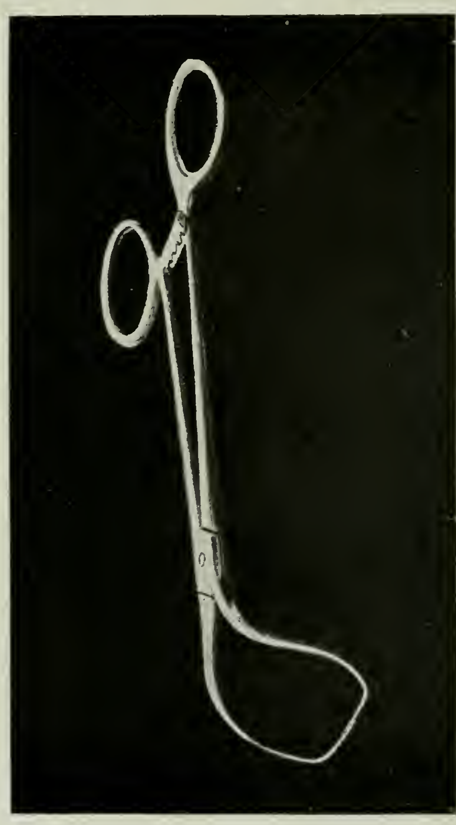


FIG. 5. SHOWS PUNCTURE CLAMP ITSELF

the exposed vas. As the vas is now superficial and fixed in the skin the lumen can be entered easily whenever desired.

Realizing that all of the previous technics require an incision and some dissection, and because of this are often refused by patients, we have devised a technic that eliminates all cutting and dissection, a technic which may be carried out in the office.

To this technic we have given the name "percutaneous puncture of the vas deferens." To insert a needle into the lumen of the vas deferens without making a cut through the scrotal skin demands an exact technic. I submit for your consideration the different instruments by means of which I have performed this operation.

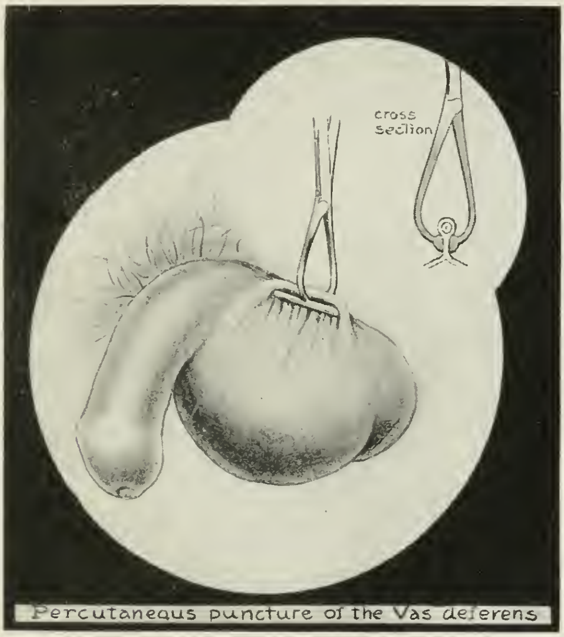


FIG. 6. SHOWS THE T CLAMP IN PLACE ON THE SCROTUM, PULLING THE VAS UP BENEATH THE SKIN AND THUS STABILIZING IT

The insert shows a cross section of the clamp, showing the relations of the scrotal skin and vas to the clamp.

1. Big clamp. To use this instrument the patient must have a long scrotum, otherwise one can not apply the clamp as the space between the testicles and the external ring is too short.

2. The puncture clamp can be used on the shortest of scrota. This instrument is an enlarged tenaculum whose teeth are at right angles to the sides of the loop of the instrument, also the teeth run by each other a goodly distance and thus make a rela-

tively straight rod. This instrument can be improvised with a large Hagedorn needle and two artery forceps.

The "T" clamp is a forceps with its two blades set at right angles to the shaft of the instrument. The shafts of the instrument are belled out so as to allow room for the fold of scrotal skin with its contained vas.

TECHNIC

Big clamp. Note the distance from the top of the testicle to the attachment of the scrotum to the pubes. If this distance is slightly longer than the width of the clamp the big clamp can be used, if not, it can not be used and either the puncture clamp or "T" clamp should be employed.

The clamp is opened wide and the testicles passed through the opening. The clamp is now closed; when it is nearly closed the scrotum and the contained spermatic cord is spread out as much as possible. This manipulation identifies the vas after which the clamp is closed moderately tight. The clamp is now held steady by an assistant and a needle inserted into the lumen of the vas following the same technic as used in puncturing veins.

Puncture clamp. To use this instrument one first picks up the vas in as small a fold of skin as possible, pulling it away from the other structures of the cord. The clamp is now so placed that its points pass through the fold of skin beneath the vas.

Next the small mass of skin in the grasp of the clamp is stretched out so that the vas is made prominent. Some traction is made on the instrument and the needle is inserted into the lumen of the vas.

"T" clamp. The vas is isolated in a fold of the scrotal skin as when we desire to use the puncture clamp. The clamp is applied loosely so as to replace the fingers. The skin is now worked down through the clamp till the skin over the vas is tense. The clamp is then tightened, traction is made upward on the clamp and the vas is ready to receive the needle.

Medicaments. An ideal medicament for injection into the vas into the infected vesicle should have the following properties:

non-corrosive to the epithelium of the vas, non-irritating to the mucosa of the vas and particularly non-irritating to the mucosa of the posterior urethra; solvent action on the secretions and exudates present, an anti-coagulant action to inhibit or prevent the normal coagulation of these secretions and lastly, a strong bac-

FIG. 7. SHOWS VAS AFTER INJECTION THROUGH ITS LUMEN OF SODIUM HYDRATE SOLUTION, SHOWING THE EXTREME NECROSIS AND DESTRUCTION DUE TO THIS INTENSELY IRRITATING SOLUTION

tericidal action. No one medicament answers all of these requirements, but the one making the closest approximation to the ideal is immune serum, the next collargol.

A solution injected into the vas deferens post-mortem flows into and fills the seminal vesicle before it discharges through the

ejaculatory duct. In life this is the sequence of events if the solution is non-irritant, but a markedly irritant injection thrown into the vas, such as 0.25 per cent sodium hydrate solution will not enter the seminal vesicle at all, but will produce a spasm of the vesicle with immediate ejaculation of its contents. With solutions that are less irritating the spasm does not occur till after some of the fluid has penetrated into the vesicle duct and even into the vesicle itself.

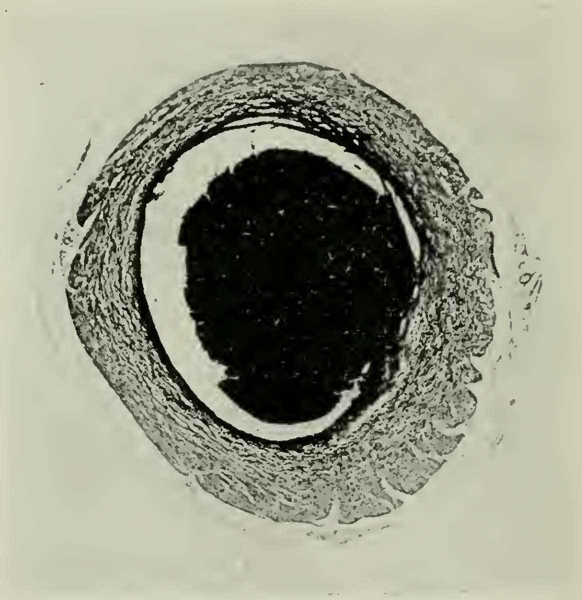


Fig. 8. Cross Section of the Vas

Through whose lumen 10 per cent colargol solution had been injected ten days previously. Note the intense staining of the mucous membrane and the colargol mass still in the lumen of the vas.

The least irritating and the medicament that enters the vesicle the best is collargol in 10 per cent strength or less. This medicament invariably enters the vesicle and distends it to a maximum. One per cent sodium bi-carbonate solution also enters the seminal vesicles well but it has only a solvent action on the vesicle secretions hence can do good only by improving the drainage

from the seminal vesicle. Five per cent sodium bicarbonate solutions destroy the epithelium of the vas but enter the vesicle well.

Acriflavine solution whose irritant action is delayed, enters the seminal vesicle fairly well, but in efficient antiseptic strength (1: 1000) it destroys the vas epithelium and consequently is not suitable for use.

Bactericidal serum has been used but little for therapeutic purposes because of its inefficiency. This is due to the great dilution of the serum by the body fluids when the serum is injected

Fig. 9. Cross Section of the Vas Through Whose Lumen 1 Per Cent Soda-Bicarbonate Had Been Injected

Note that the epithelium is intact

subcutaneously. The only instance of therapeutic success in using a bactericidal serum is the treatment of epidemic meningitis with meningococci serum injected into the subarachnoid space. In this disease the serum is injected into a closed sac, the dura, which also harbors the causative organism. Absorption from this sac is very slow and consequently in epidemic meningitis the pathology and physical conditions for the action of a bactericidal serum are ideal; namely, non-dilution of the serum, prolonged contact with the bacteria both free in the cavity and in the wall

FIG. 10. CROSS SECTION OF THE VAS THROUGH WHOSE LUMEN 1-1000 ACRIFLAVINE SOLUTION HAD BEEN INJECTED, ONE HOUR BEFORE DEATH

Note that in a very few places the epithelium has been destroyed

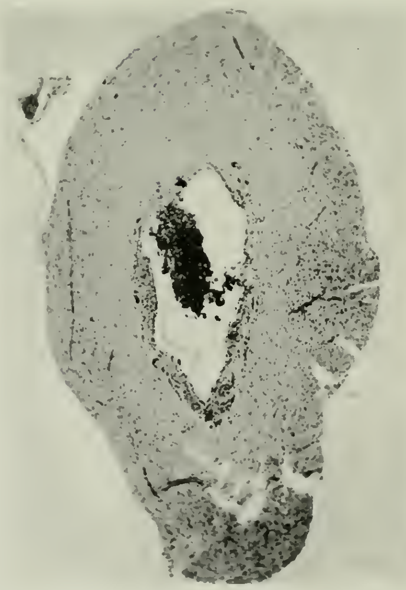


FIG. 11. CROSS SECTION OF THE VAS INTO WHOSE LUMEN 1-1000 ACRIFLAVINE WAS INJECTED THREE DAYS PREVIOUSLY

Note complete destruction of the epithelium lining the vas

as the serum is absorbed. The same conditions to a great extent prevail in the seminal vesicles.

Bactericidal serum from the theoretical standpoint is the ideal antiseptic; from a practical standpoint its efficiency is high if its mode of action and conditions appropriate to this action are

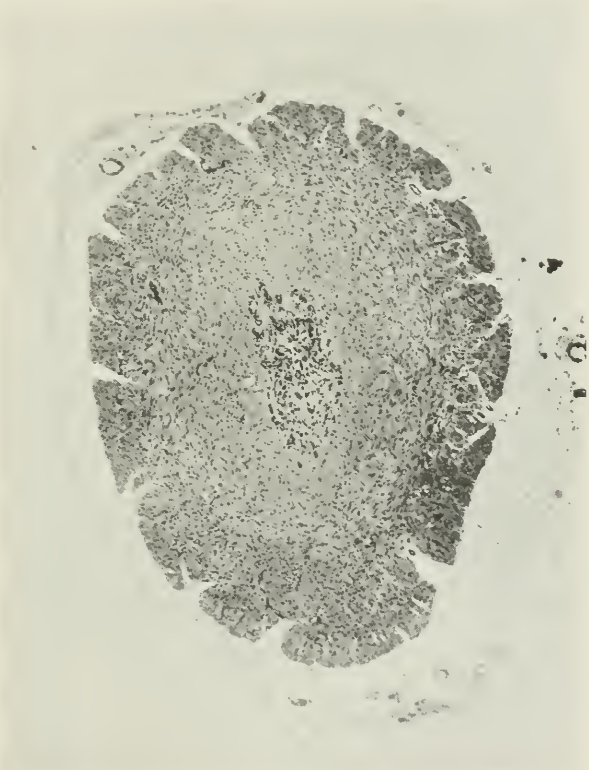


Fig. 12. Cross Section of the Vas Into Whose Lumen 1–1000 Acriflavine Had Been Injected Five Days Previously

Note the almost complete destruction of the epithelium and obliteration of the vas lumen.

present or produced. For bactericidal serum to be effective complement must be present. In the clinical use of bactericidal serum complement is usually present in sufficient amount in the patients own serum. If the conditions necessitate, as they do

in the seminal vesicle, a surface action or a bactericidal effect upon the contents of the vesicle where the patients serum will not be available, one had best mix some fresh blood serum, either human or animal, with the immune serum at the time of injection.

Fig. 13. Cross Section of the Vas Through Whose Lumen 1–1000 Acriflavin Had Been Injected Seven Days Before

Note almost complete destruction of the epithelium and obliteration of the lumen.

I have used bactericidal serum (antigonococcic) in the treatment of acute anterior urethritis, but the technics necessary to overcome the anatomical arrangement were so difficult that the attempt was given up.

In the treatment of chronic seminal vesiculitis however, I have used bactericidal serum, at first plain and later with the addition of fresh serum. Bactericidal serum can be injected into the seminal vesicle by any of the ordinary methods of vasostomy, but the field in which it is the antiseptic par excellence is when it is administered by my technic of percutaneous puncture of the vas. No solution that is irritating to the tissues can be used with this

Fig. 14. Seminal Vesicle Casts Due to Chronic Infections Expressed by Rectal Manipulations of the Seminal Vesicles

These casts are very common in chronic vesiculitis

technic as yet as it has not been developed to a point that we can be absolutely certain of entering the vas lumen. When the ordinary medicaments are used and we do not enter the vas lumen, one will have a marked tissue irritation in the structures surrounding the vas. With bactericidal serum if one does not enter the lumen of the vas, no pain or trouble will ensue as then we have simply given a subcutaneous dose of gonococcic serum.

Bactericidal serum is absolutely specific, hence if we expect to obtain results by its use, one must use the specific serum, for

whatever organism is present, or if we know or believe that multiple organisms are causing the infection, we must use a multiple serum. The bacteriology of acute seminal vesiculitis is probably gonococcic but the bacteriology of chronic seminal vesiculitis has not yet been worked out to an absolute end, but in all the published reports of examinations most of the common pus organisms are found and the gonococcus only in a minority of the cases. In fact many of the vesicles are sterile even when examined by grinding the vesicle wall in sand.

CONCLUSIONS

Puncture of the vas deferens and injection of fluids through it into the seminal vesicle is possible without cutting the skin. Acriflavine solutions in 1:1000 strength destroy the epithelium of the vas and hence can not be used.

Sodium bicarbonate solution in 1 per cent strength is proper and safe. In 5 per cent solution it is destructive to the epithelium of the vas. The only medicament that can be used safely by means of percutaneous puncture of the vas is bactericidal serum.

ANATOMICAL, EMBRYOLOGICAL AND PHYSIOLOGICAL STUDIES OF THE TRIGONE AND NECK OF THE BLADDER

MILEY B. WESSON

From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital

The mechanism of micturition remains obscure in spite of the many theories advanced to explain it. All these theories have been shown to be unsatisfactory and it is common to all of them that they are founded upon incomplete anatomical knowledge. The trigonal muscle, on account of its peculiar anatomy and close relationship to the vesical orifice, has been the subject of much interest in this connection. Cystoscopic observations show that it contracts during efforts to empty the bladder, pulling the verumontanum upward.

The so-called vesical sphincters have never been exactly delimited anatomically. Physiologically it is known that both of these "sphincters" must be destroyed before incontinence supervenes, either being able alone to maintain continence. During a consideration of these elements, it became evident that exact anatomical studies of the region under discussion were indispensable to any advance in our knowledge. The present paper is an effort to realize these studies. The structures have been followed during embryological development, and a series of cystoscopic and pharmacological studies on the processes involved in micturition also included.

Sir Charles Bell (1) in 1812 first called attention to the existence of muscle bundles flowing downward from the ureters to the vesical orifice. These bundles have since been known by his name. Ellis (2) in 1856 confirmed this work, describing a submucous layer joining the ureteral orifices with the longitudinal coats of the urethra. According to Walker (3) this longitudinal layer of nonstriated muscle which lies beneath the bladder mucous

membrane is separated from the circular muscle by a thin layer of loose areolar tissue passing forward as far as the vesical orifice where it dips down to form the internal longitudinal layer of the floor of the urethra.

Kalischer (4) regards the sphincter (M. sphincter trigonalis) as made up of two divisions; one lying in the bladder which is fan-shaped, the other in the prostatic urethra which is of circular outline. These latter have their origin in the muscle bundles lying beneath the trigone. They pass obliquely downward and forward and surround the urethra in an oblique direction. The fibers are best developed near the bladder, becoming progressively thinner and finally disappearing in the lower third of the prostatic urethra. Frisch and Zuckerkandl (5) do not share Kalischer's opinion regarding the bladder portion. They believe that only the wedge shaped portion of the trigone abutting upon the urethral orifice should be regarded as the vesical part of the sphincter, as the rest of the muscle would be at a disadvantage as regards sphincter action when flattened out in the distended bladder. Griffith (6), Quain (7) and Metzner (8) differ on this point in degree only. Kohlrausch (9) advocated the old theory that the vesical orifice was funnel-shaped, and that the sphincter was a continuation downward of the circular musculature of the bladder; the fibers of the external longitudinal muscle (detrusor urinae), which inserted at right angles into the internal sphincter were supposed during contraction to pull upon the sphincter and cause it to open. Versari (10, 11) later reiterated this view. He believed that the internal vesical sphincter is made up of an urethral and a trigonal portion, and that it is the urethral portion only which assumes the form of a ring surrounding the initial part of the urethra. The muscles of the posterior segment of the urethral portion extend upward to occupy part of the trigonal area and downward, along the posterior wall of the urethra. Zuckerkandl (12) on the contrary, held that the trigonal fibers passed through or over the sphincter and had no effect on it. The great objection to Kohlrausch's theory is, according to Kelly and Burnam, that it is not possible for the weak external layer or detrusor

to pull open the strong sphincter. They believe that it may give an impulse to the sphincter which results in its relaxation.

The topography of the trigone has been described in great detail by various writers. Griffith (14) found the trigone to be distinct only in man and monkeys and therefore concluded that it had some relation to the erect posture. Elliott, however, described in cats, dogs and rabbits a superficial sheet of muscle spreading up from the urethra in all cases as far as the ureters, innervated by sympathetic nerves which cause its contraction. In pigs we found that the ureteral openings were very close to the internal vesical orifice, but there was a definite trigonal muscle which connected the two ureters and flowed down the urethra. When it was dissected free, the fibers were found to be intimately associated with the large verumontanum. In dogs the trigone corresponded in size with that of a newborn baby, but though Bell's muscles were very prominent, there was no Mercier's bar. The fibers flowed from the ureters straight down through the vesical orifice, so that the trigone was "V" shaped instead of triangular.

According to Eteau (15) the trigone is an equilateral or isoseles triangle in infants and a scalene triangle in adults, the difference in the length of the sides being greater in males than in females. Schewkumuko (16) found that the width varies with that of the pelvis, being greatest in fat women, and that all markings are lost in multipara suffering from cystocele. Testut (17) called attention to the fact that the right side of the trigone is slightly longer than the left and ascribes this asymmetry to the presence of the rectum and sigmoid.

The location of the ureteral orifices is subject to great variation. Eteau found that the maximum interureteral distance in the male was 88 mm., the average 32.7 mm., while the distance from the ureteral orifice to the neck of the bladder ranged from 61 mm. to 10 mm. A review of the literature of anomalies both as to position and number of ureteral orifices indicates that both orifices are never present on the same side of the median line (15). Where supernumerary ureters are present the ureteral meatus usually lies on the trigone (18), but exceptions have been

reported by Cecil (19) and Mertz (20). Schewkumuko in his series of bladders, found supplementary ureters in 3 per cent of females and in 1.5 per cent of males. They all occurred on the left side, opening near the midline, and the trigone was always asymmetrical. Delbet (21) states that in congenital absence of the ureter, the corresponding side of the trigone is lacking. Passavant and Young (22) reported cases in which the trigone had been dissected free from the bladder wall.

MATERIAL AND METHODS

The material used for microscopic study is indicated in the accompanying table. Microscopic measurements were made with a Spencer ocular micrometer calibrated with a Zeiss micrometer stage objective. The early stages of development were obtained from the collection of the Carnegie Institute of Embryology, while for the older stages, preparations were made from material obtained from the Pathological Department of the Johns Hopkins Hospital. The bladders removed at autopsy were injected with 10 per cent formalin and then hardened in a jar of this solution. In order to avoid fixation of an overdistended bladder, the injection was made through the urethra, the meatus being closed with a pair of thumb forceps, until the bladder was immersed in a jar of 10 per cent formalin. If the bladder was overdistended, the excess would be expelled as soon as the specimen was released and the bladder would be fixed fully dilated. After twenty-four hours, a window was cut in the apex, the bladder contents emptied, and the fixed specimen then preserved in clean formalin. Tying off the urethra is entirely unnecessary, and not only mutilates the specimen but causes fixation in an overdistended state.

Special preparations of the trigone were made by means of the acetic acid method of Mall (23). After prolonged immersion in 5 per cent acetic acid, the elastic tissue which binds the trigone to the circular bladder muscle swells, facilitating their separation. The mucous membrane which is removed first is much more adherent over the trigone than elsewhere. The ureters are then

Table of Specimens Studied Microscopically

CROWN RUMP LENGTH	CARNEGIE INSTITUTE NUMBER	ESTIMATED MENSTRUAL AGE	SEX	THICKNESS OF SECTIONS	DIRECTION	STAIN	SOURCE
mm.		*weeks*		*microns*			
3.5	186	4		20	Oblique	Cochineal	Carnegie
3.9	463	4		10	Transverse	Cochineal	Carnegie
4.0	808	4		15	Transverse	H. and E. H. E. Au. and Or. G. Van Giesen Cochineal	Carnegie
4.3	148	4		10	Transverse	H. and E.	Carnegie
6.0	988	5		20	Transverse	Cochineal	Carnegie
6.0	241	5		10	Transverse	H. and E.	Carnegie
6.6	371	5		10	Sagittal	Cochineal	Carnegie
9.0	422	5		40	Transverse	Carmine	Carnegie
9.0	452	5		40	Sagittal	Carmine	Carnegie
9.0	721	5		15	Transverse	H. and E.	Carnegie
9.0	887	5		40	Transverse	Cochineal	Carnegie
10.0	1197	5		20	Sagittal	H. E. Au. and Or. G.	Carnegie
13.0	485	6		40	Coronal	Cochineal	Carnegie
13.5	695	6		10	Transverse	H. and congo red	Carnegie
20.0	462	7		40	Transverse	Cochineal	Carnegie
21.0	460	7		40	Transverse	H. and E. Cochineal	Carnegie
23.0	966	8		40	Coronal	Cochineal	Carnegie
26.0	782	8		5 to 40	Transverse	H. and E. H. E. Au. and Or. G. Cochineal Iron Haem.	
35.0	210	9		50	Transverse	H. E. Au. and Or. G.	Carnegie
67.0	1656	12	Male	200	Sagittal	Cochineal	Carnegie
80.0	34	13½	Male	50	Transverse	Cochineal	Carnegie
80.0	172	13½	Male	100	Transverse	Cochineal	Carnegie
80.3	768c.	13½	Male	6	Transverse	H. and E.	Carnegie
130.0	1018	17	Male	50	Transverse	H. and E.	Carnegie
161.4	1049	20	Male	40	Transverse	H. and E.	Carnegie
221.0	1172	25	Male	15	Transverse	H. and E.	Carnegie
240.0	2671a†	27	Male	10, 16	Transverse	H. and E.	Path. Dept.
240.0	2671b†	27	Male	10, 16	Sagittal	H. and E.	Path. Dept.
276.0	2607	30	Male	40	Transverse	H. and E.	Carnegie
500.0 C. H.	2679	Term	Male	14	Transverse	Differential*	Path. Dept.
—	3031	Term	Female	14	Sagittal	H. and E.	Obst. Dept.
Adult	2911‡	43 yrs.	Male	20	Sagittal	Differential*	Path. Dept.
Adult	2778	49 yrs.	Male	20	Sagittal	Differential*	Path. Dept.

* Differential stains: Mallory; orcein; phosphotungstic acid-iron haematoxylin; haematoxylin, borax-iron ferrocyanide; haematoxylin and eosin; haematoxylin, eosin, aurantia and orange G; Weigert; Weigert and picric acid; and Van Giesen.

† Twins.

‡ Early median bar.

dissected free with Mercier's bar and later the entire trigonal muscle raised. The planes of cleavage are quite readily followed because of the separation of mucosa, trigonal muscle and the heavy circular muscle by layers of blood vessels. Macerated specimens of the neck of the bladder were prepared by boiling one-half hour in 5 per cent hydrochloric acid, after which the muscle fibers were teased out with needles.

Glass models were made of the neck of the bladder of specimen 2671b, a seven and one-half months fetus, cut sagitally, and of specimen 2679, a term fetus, cut transversely. An Edinger projection apparatus was used and the sections drawn upon glass plates. Distortion of the model was prevented by keeping the magnification in proportion to the thickness of the sections and of the glass plates. The sections were traced directly on glass, using various colored Higgins' inks. In order to facilitate their easy handling, the model was divided into units one and one-half inches thick, each being bound tightly with adhesive tape.

EMBRYOLOGY OF THE TRIGONE

The trigone of the bladder (tr. Lieutaudii) is a smooth triangular area lying in the base of the bladder, having the two ureters and the vesical orifice at its angles. It is better to conceive of the trigone as a region rather than to assign this name to any structure or structures. In the trigonal region are the two muscle layers of the bladder wall, the external longitudinal and the internal circular, and superimposed upon these is the submucous or trigonal muscle, which is an expansion of the longitudinal muscle layer of the ureters and their sheaths extending downward and passing into the urethra. The mucous membrane is smooth and velvet-like. Being more vascular than the remainder of the bladder, its color is a deeper red. Occasionally, subtrigonal or Home's glands are found near the vesical orifice. Treves (24) found that the mucous membrane of the trigone differs from that of the remainder of the bladder in that it is so firmly adherent to the subjacent tissue as to present rarely any rugae even when the bladder is empty,

thus preventing prolapsus of the mucous membrane into the vesical orifice during micturition.

The adventitia of the ureter, beginning several centimeters above the bladder, is strengthened and thickened on the dorsal side by robust longitudinal bundles of involuntary muscle that follow the ducts to their vesical ends, and in conjunction with the fibrous tissue in which they are embedded, form Waldeyer's (25, 26) ureteral sheath. From this sheath bands of muscles (Bell's muscle) pass toward the vesical orifice along each side of the trigone while others (Mercier's bar) unite the orifices forming the base of the triangle. These fibers are probably a continuation of the longitudinal muscles of the ureters or of Waldeyer's sheath. Satani (27) found that immediately after the ureter enters the bladder wall, the circular fibers are lost, leaving only the longitudinal fibers, the external and internal layers being now in apposition. These gradually disappear on the medial side of the muscle layer, leaving a half circle surrounding only the outer side of the tube; at the ureteral orifice the longitudinal layer disappears almost entirely.

The vesical orifice is generally circular in outline and has, as a rule, a number of fine lines or folds radiating from the center of the opening. The central fold which has been known as the uvula of Lieutaud is a slight elevation of mucous membrane which extends forward from the middle of Mercier's bar to the posterior margin of the urethral orifice. In its natural state it may contribute to the more perfect closure of the orifice of the bladder. When it undergoes hypertrophy, it may exert a valve-like action and completely obstruct the vesical orifice.

The vesical trigone is developed from the wall of the primary excretory duct which runs beneath the ectoderm in the angle between the urogenital fold and the parietal mesoblasts to a point caudal to the middle of the cloacal membrane. There it bends horizontally and reaches the lateral wall at the junction of the middle and lower thirds of the cloaca, the cloaca being that portion of the posterior intestinal bay that lies caudal to the point where the allantois is given off. Into it there open

above the end-gut and the allantois. Felix (28) found that the primary excretory duct was solid and that its free terminal portion had reached the cloaca in an embryo 4.25 mm. vertex-breech length, and at 7 mm. it had penetrated the cloaca. Keibel, however, noted this in a 4.2-mm. embryo. We found in a 3.5-mm. embryo that the duct reached the cloaca as a tube with an

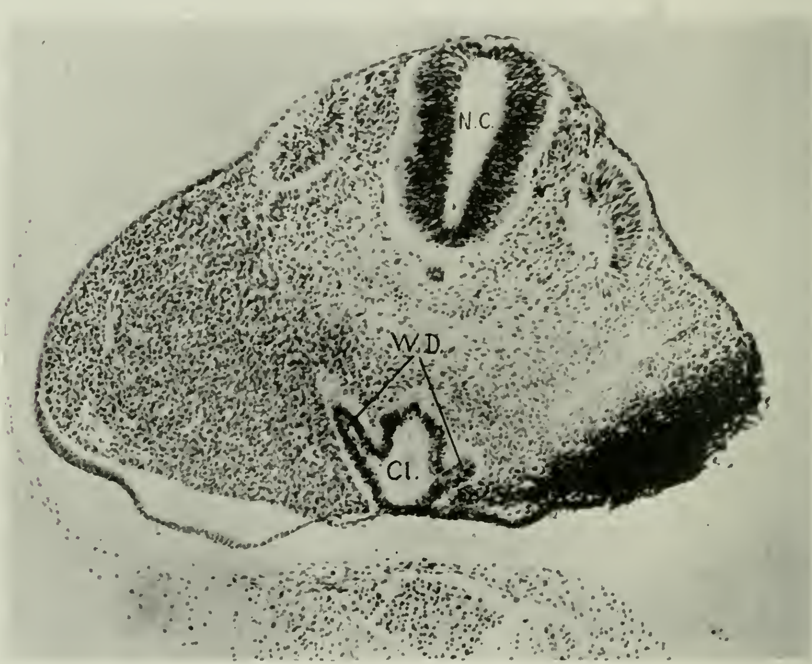


Fig. 1. Cross Section Through Caudal End of a 4.3 mm. Human Embryo

Shows both Wolffian ducts entering the cloaca. *W.D.*, Wolffian duct; *N.C.*, neural canal; *Cl.*, cloaca. Embryo, Carnegie Institute 148, slide 7, row 1, section 13. × 100.

apparently blind end into which the cloacal wall does not invaginate. But in an embryo of 3.9 mm. total length, the excretory duct is seen to enter the cloaca. This is shown even better in an embryo of 4.3 mm. total length (fig. 1). However, the stage of development cannot be accurately gauged by the length of the embryo, for in one of 4 mm. total length, the excretory ducts still showed as solid masses, touching the cloacal membrane.

In a 6-mm. embryo, the ureteral bud appears. At the sagittal bend made by the excretory duct before it reaches the cloaca, there is an enlargement and a localized thickening throughout the entire circumference, which is the origin of the ureter. This is near the medial surface on the dorsal side, but as it elongates to form a canal, it inclines more and more toward the lateral surface. At first, this short ureteral bud grows dorsally toward the vertebral column, but in a 9-mm. embryo it has formed a curve and is growing cranially. This curve quickly flattens out as the ureteral bud rises.

The absorption of the common duct into the allantois may be conceived as an expansion of the common duct until it is flattened out and is incorporated into the wall of the cloaca. Thus it will be seen that there is a small portion of the wall of the primitive bladder that has originated in quite a different manner from the remainder, namely from the mesoderm. This process begins in embryos between 5.3 mm. and 7 mm. greatest length. The absorption does not take place synchronously on the two sides. In a 6-mm. embryo one terminal common duct is 0.16 mm. long and the other only 0.05 mm. long. The gut lies closer to the longer one and empties 0.03 mm. below it. In two 9-mm. embryos, 422 and 887, the process was complete, the Wolffian ducts and ureters meeting at the cloacal wall, but in embryo 721, of the same length, a common duct 0.075 mm. long persisted. When the terminal portion of the primary excretory duct has been completely absorbed and the direct communication of the ureter with the bladder established, the ureter lies immediately lateral to the opening of the Wolffian duct. As development proceeds, the ureteral orifices come to lie upward and outward in relation to the opening of the Wolffian ducts which remain close together. This process may very well be due to a further opening out of the ureters themselves similar to the process that took place with the common duct. In any case the tissue in the area between the opening of the Wolffian ducts and the ureters is of mesodermal origin and with the lateral displacement of the ureteral orifices begins to assume a triangular form and is the primitive trigone. The region about the orifices

of the Wolffian ducts becomes raised and forms Müllers hillock, the early verumontanum (fig. 2). In a 13-mm. embryo craniolateral migration of the ureters has begun (fig. 3), and in a 13.5-mm. embryo has so far progressed that each ureteral opening is 0.04 mm. craniolateral to that of the corresponding Wolffian

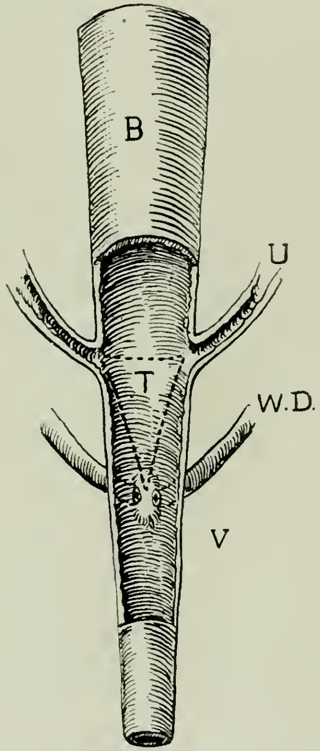


Fig. 2. Diagram of a Bladder of 20 mm. Human Embryo

B., bladder; *U*, ureter; *W.D.*, Wolffian duct; *T.*, trigone; *V.*, Müller's hillock or verumontanum.

duct. By the time the embryo has reached 21 mm. total length, the trigone forms an equilateral triangle, each side of which measures 0.36 mm. A transverse section of the bladder presents an appearance similar to a half-moon, and while we found that occasionally the ureters entered at the tips of the half-moon

as commonly described, in most cases they entered on the dorsal aspect about 0.03 mm. from the tips. This relation is well shown in figure 4. At 80 mm. the ureters enter the bladder in an oblique direction (fig. 5). The separation of the urethra from the bladder takes place gradually. In a 21-mm. embryo, the bladder portion has enlarged till it is twice the diameter of

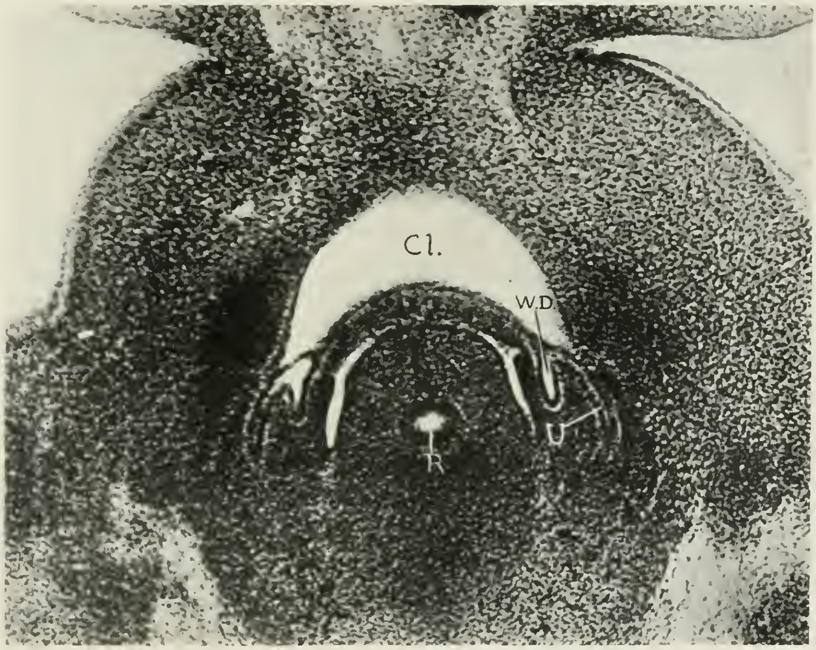


Fig. 3. Cross Section of a 13 mm. Human Embryo

Showing cranio-lateral migration of ureters. *R.*, rectum; *W.D.*, Wolffian duct; *U.*, ureter; *Cl.*, cloaca. Embryo, Carnegie Institute 485, slide 5, row 3, section 4. × 100.

the urethra and is cone-shaped, while in a 23-mm. embryo there is a definite enlargement cranial to Müllers hillock, giving an appearance similar to that of the adult bladder and urethra (fig. 6).

The observations made on the gross specimens studied show that no rules can be deduced as to shape and size of the trigone,

as they display great individual variations independent of age, sex or size of bladder. This is well-shown by plates 1 and 2 which are reproductions of life-size drawings.

Specimens prepared by Mall's method of softening the elastic tissue, show the trigonal muscle to be very thin in the center and made up of fibers flowing down from the ureters and inter-

FIG. 4. CROSS SECTION OF A 21 MM. HUMAN EMBRYO

The ureters enter on the dorsal surface of the bladder (cloaca) and not at the lateral edge. *Cl.*, cloaca; *U.*, ureter. Embryo, Carnegie Institute 460, slide 34, row 2, section 1. × 300.

lacing with those from the opposite side. The lateral boundaries of the triangle are not sharp as some of the fibers run out at right angles to Bell's muscle for a short distance. Mercier's bar is very thick and seems to lie in a depression of the circular layer below. The relationship of the trigonal muscle to the circular and longitudinal layers is clearly shown in plate 3.

In the very early embryos the entire primitive vesico-urethral tract is lined by a single layer of cylindrical epithelium, vesicular in type, practically all of the nuclei lying nearer the periphery of the cells. In a 13-mm. embryo this epithelium below the ureteral openings (vesical trigone) consists of two or three layers, and in 40-mm. embryo of four or five layers, while that of the

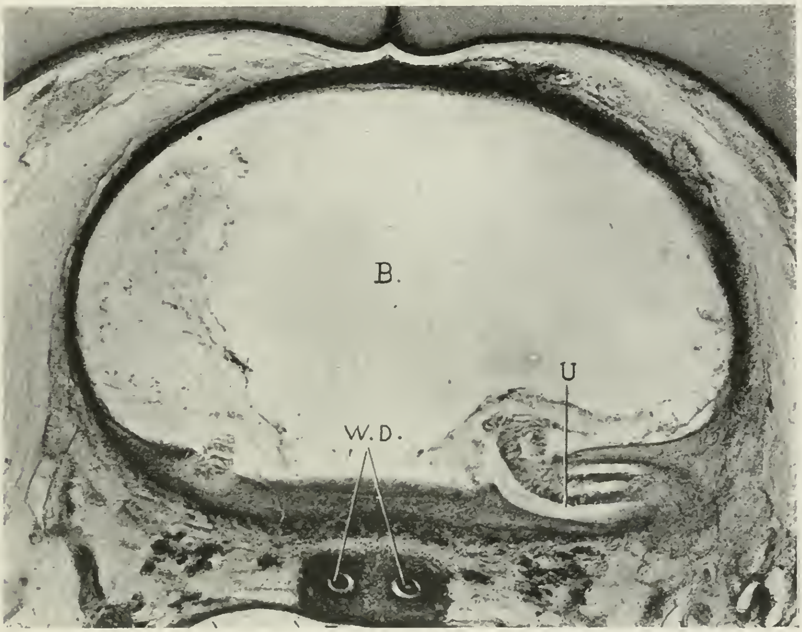


FIG. 5. CROSS SECTION OF A 80 MM. MALE EMBRYO

Shows the ureters entering the bladder in an oblique direction. *U.*, ureter; *B.*, bladder; *W.D.*, Wolffian ducts. Embryo, Carnegie Institute 24, slide 51, row 2, section 4. × 30.

remainder of the bladder is composed of two layers. The cells are not uniform in shape but vary in different embryos from high cylindrical to low cuboidal. The superficial cells show marked mitosis, some contain two nuclei, and in all cases they retain their vesicular character, the nuclei being near the surface of the cell. In later stages the cells of the lower-most layer are

regular in outline and the nuclei small and located in the center of the cells. As the cells approach the surface they become transitional in type and fusiform in outline with large, oval and faintly staining nuclei. In still later specimens the cells often appear to be arranged in perpendicular rows.

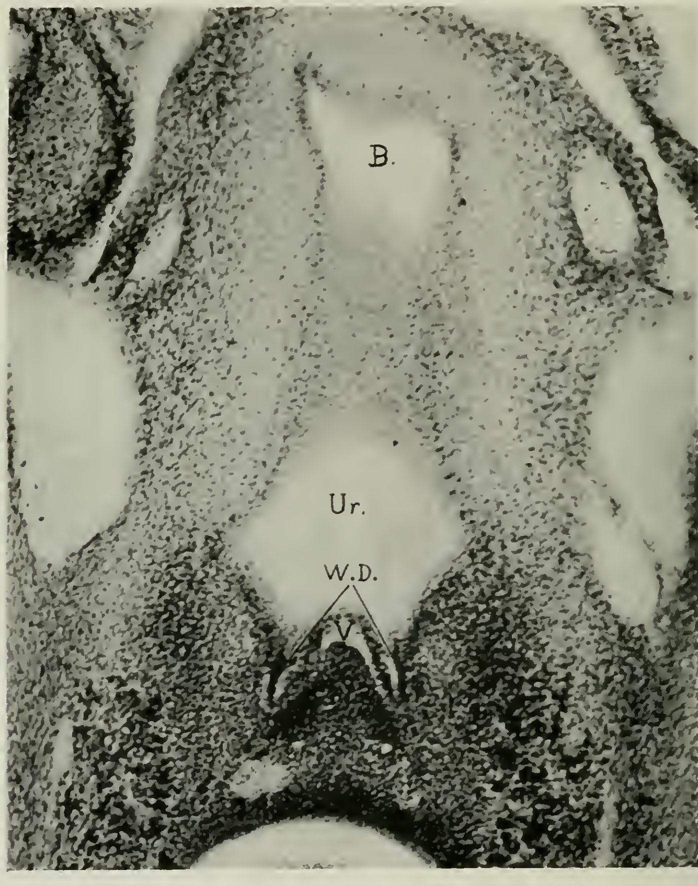


Fig. 6. Cross Section of a 23-mm. Human Embryo

Shows the beginning separation between the urethra and bladder. The section proximal shows bladder alone and the one distal urethra. *V.*, Müller's hillock or verumontanum; *W.D.*, Wolffian ducts; *B.*, bladder; *Ur.*, urethra. Embryo, Carnegie Institute 966, slide 13, row 1, section 2. × 100.

The cells of the urethra multiply faster than those of the bladder; hence, they are smaller and more closely packed together, giving to the stained sections of the urethra a darker appearance than that seen in sections of the fundus of the bladder. Finally, the cells of the superficial layers of the bladder lose their vesicular character and become cuboidal. In a 35-mm. embryo the verumontanum is covered with a single row of cuboidal cells which becomes double as the ejaculatory ducts are approached and four or five layers deep on the dorsum of the urethra. As the embryo increases in size, the number of cells over the verumontanum becomes greater and in a 70-mm. embryo they are three or four layers deep.

Lowsley (29) and Watson (30) found that a condensation of loose mesenchyme tissue precedes the formation of the musculature, the direction of the young cells suggesting their later developments as longitudinal or circular fibers. This condensation begins at the apex of the bladder and proceeds toward the orifice of the urethra. Below the opening of the ureters, the earliest formed musculature is always in a single layer and is composed of circular fibers. It is to be seen first in a 20-mm. embryo and its development is well advanced in a 26-mm. embryo. In this embryo there is also a dense longitudinal condensation of mesenchyme fibers along the terminal portions of the ureters. These fibers continue posteriorly to anastamose with those of the opposite side subsequently occupying the position of Mercier's bar. Other mesenchyme fibers pass downward as two bundles from the ureters toward Müllers hillock and probably represent Bell's muscles.

EMBRYOLOGY AND ANATOMY OF THE MUSCULATURE OF THE VESICAL NECK

The bladder has an internal circular and an external longitudinal layer of smooth muscle, which are not perfectly defined. Confusion is increased by the fact to which Howell (31) calls attention, that the direction of these fibers and the number of layers into which they can be separated depends to a large

extent upon the state of distension of the bladder, as the muscle fibers rearrange themselves during changes in the size of the bladder.

In the trigonal region there is in addition the trigonal muscle. The trigonal muscle consists of fibers extending fanwise from the

Fig. 7. Sagittal Section Through Vesical Orifice of Adult

The elastic tissue fibers from the external longitudinal muscle bundles pass upward through the circular layer and end below the trigonal muscle. *P.*, prostate; *L.M.*, longitudinal muscle; *C.M.*, circular muscle; *T.M.*, trigonal muscle. Specimen, Carnegie Institute 2778, slide 3, section 2. × 10.

ureteral orifices, some fibers passing medially, going to make up Mercier's bar, others interlacing with corresponding fibers from the opposite side in the middle of the trigone, and still others passing directly down to the urethra and making up Bell's muscles. The Bell's muscles of the two sides coverge at the vesical orifice, causing the trigonal muscle at this point

to be denser and thicker. Where the thickened layer passes over the edge of the vesical orifice, it makes up the principal portion of the uvula of Lieutaud. Below the vesical orifice the fibers pass downward along the urethra, thinning out to form an internal longitudinal layer on the floor of the prostatic urethra.

Behind the interureteral ridge the circular layer of the bladder is made up of large loose bundles of muscle fibers but as it passes under Mercier's bar, the character of the muscle changes and the bundles become smaller and more compact. Similarly, the longitudinal bundles become more compact as they sweep beneath the trigone up toward the vesical orifice. They are surrounded by elastic fibers, which, as the muscle tapers off and ends, pass on through the circular layer becoming lost at its upper edge. Their direction is practically perpendicular to that of the trigonal muscle. It appears as though these fibrils form a sort of attachment or tendon for the muscle fibers which end in this region. They are very well shown in a photomicrograph which is reproduced as figure 7.

In considering the muscular mechanism, making up what has been called the internal sphincter of the bladder, the reader is referred to plate 4 and the accompanying diagram (fig. 8). Various stages in the development of this mechanism have been followed through the embryos of this series. The principal elements are however well shown in the diagram and a reference to it will enable the reader to orient himself with regard to this complicated arrangement. The details of the exact distribution of the muscle fibers have been studied by means of glass plate reconstructions and macerated specimens, neither of which unfortunately lend themselves to pictorial reproduction.

The fibers of the external longitudinal layer sweep down along the surface of the bladder until they reach the region of the vesical orifice where many of them end. The elastic fibers as mentioned above continue on and form a sort of tendinous arrangement connecting with the denser layers about the vesical orifice. A portion, however, of those fibers which sweep along the back of the bladder, are diverted from the general course of the other fibers, dropping slightly away from the lumen of

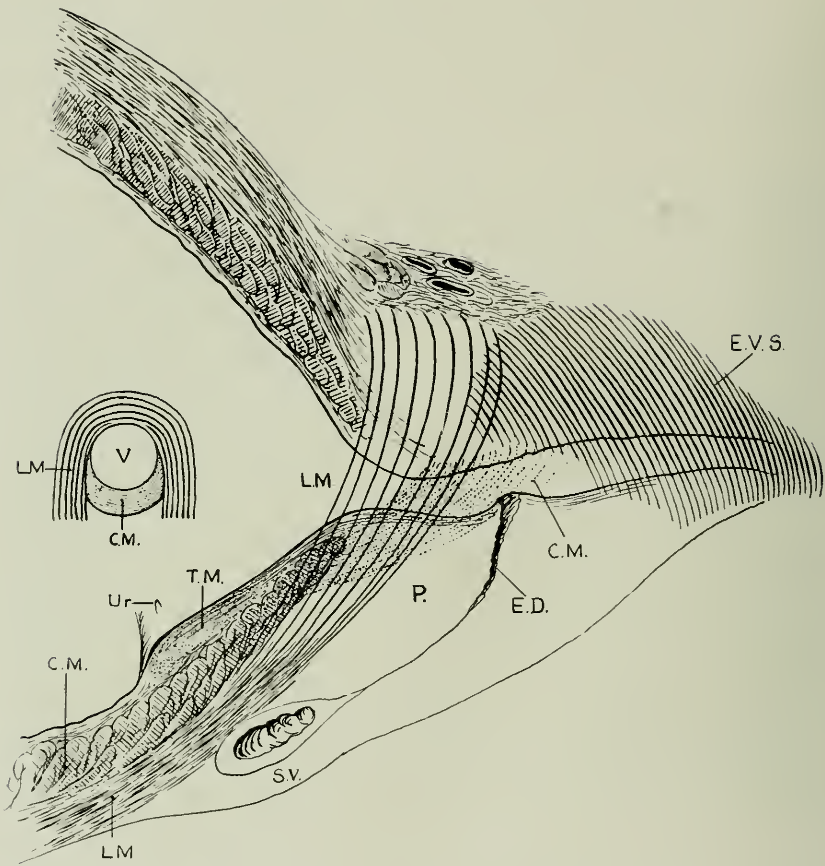


FIG. 8. SAGITTAL SECTION OF BLADDER OF ADULT

Diagram of plate 4. The external longitudinal layer of the base sweeps up over the vesical orifice, making a loop. Within this loop the circular layer forms a wedge below the orifice and flows down the urethra in an oblique direction surrounding the canal as a thin layer. The result is a double loop and not a sphincter. The small insert is a cross section of the vesical orifice, showing the upward pull of the loop from the circular muscle and the opposing action of the longitudinal muscle loop. *V.*, vesical orifice; *L.M.*, longitudinal muscle; *C.M.*, circular muscle; *T.M.*, trigonal muscle; *E.V.S.*, external vesical sphincter (striated muscle); *Ur.*, ureteral orifice; *S.V.*, seminal vesicle; *E.D.*, ejaculatory duct; *P.*, prostate.

the bladder and passing forward between the prostate and bladder mucosa. They diverge slightly to form muscular bands which pass forward and downward on either side of the urethra. At the upper level of the urethra these two bands swing medially and unite to form a loop or arch about the urethra (fig. 9). The

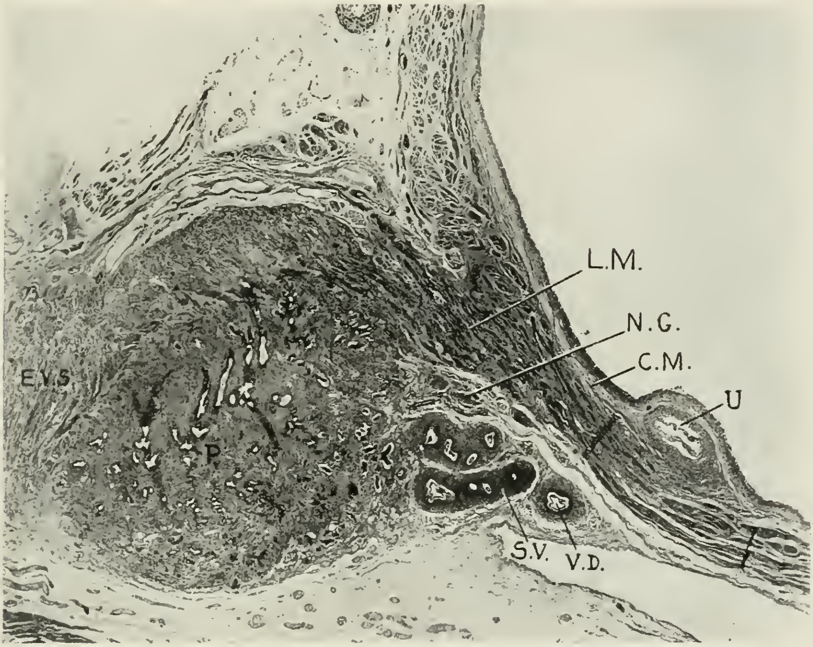


Fig. 9. A Sagittal Section Through Lateral Lobe of Prostate of 240-mm. Human Embryo

The longitudinal layer of the base is sweeping out over the urethra making a crus over the orifice. *U.*, ureter; *S.V.*, seminal vesicle; *V.D.*, vas deferens; *P.*, prostate; *E.V.S.*, external vesical sphincter; *L.M.*, longitudinal muscle; *C.M.*, circular muscle; *N.G.*, nerve ganglia. Embryo, Carnegie Institute 2671b, slide 46, row 2, section 1. × 10.

fibers pass freely through this loop and there is no raphé formation. A cross section of this loop, where it passes in front of the urethra, is shown in the diagram. The fibers sweeping down the anterior surface end for the most part as described above at the vesical orifice, but a few pass along the anterior aspect of the prostatic

urethra just beneath the mucosa, forming an internal longitudinal layer of the urethra, corresponding to the trigonal fibers on the posterior aspect (fig. 10).

The circular fibers pass around the bladder until a point is reached just opposite the vesical neck. Here some of the fibers

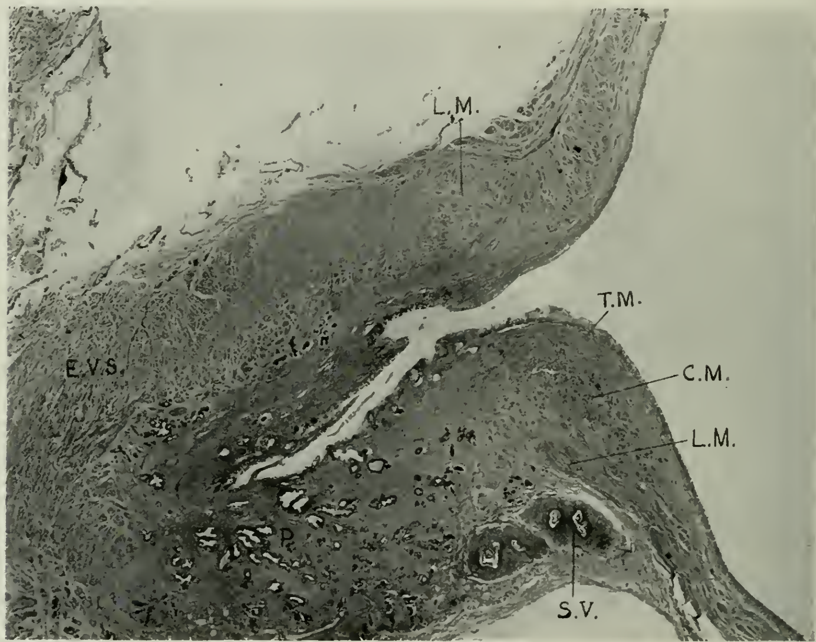


FIG. 10. SAGITTAL SECTION THROUGH VESICAL ORIFICE OF 240-MM. HUMAN EMBRYO

T., trigonal muscle; *S.V.*, seminal vesicle; *P.*, prostate; *E.V.S.*, external vesical sphincter; *L.M.*, longitudinal muscle; *C.M.*, circular muscle. Embryo, Carnegie Institute 2671b, slide 93, row 2, section 2. × 10.

from the region posterior to the vesical orifice swing downward and forward in an oblique direction, passing as thin bands inside of the loop of the external longitudinal muscle described above and swinging around the urethra in the region generally opposite the verumontanum where they also form a loop or arch in front of the urethra. This arrangement leaves a short length of the

urethra extending from the vesical orifice about half way down to the verumontanum, without any investment of fibers arising from the internal circular layer (fig. 11). Other fibers branching off from this band as it passes downward and forward in its oblique course, extend into the prostate gland. Their course cannot be followed among the prostatic tubules. It seems probable, however, that the prostate represents the posterior portion of this collection of circular fibers extending down around the

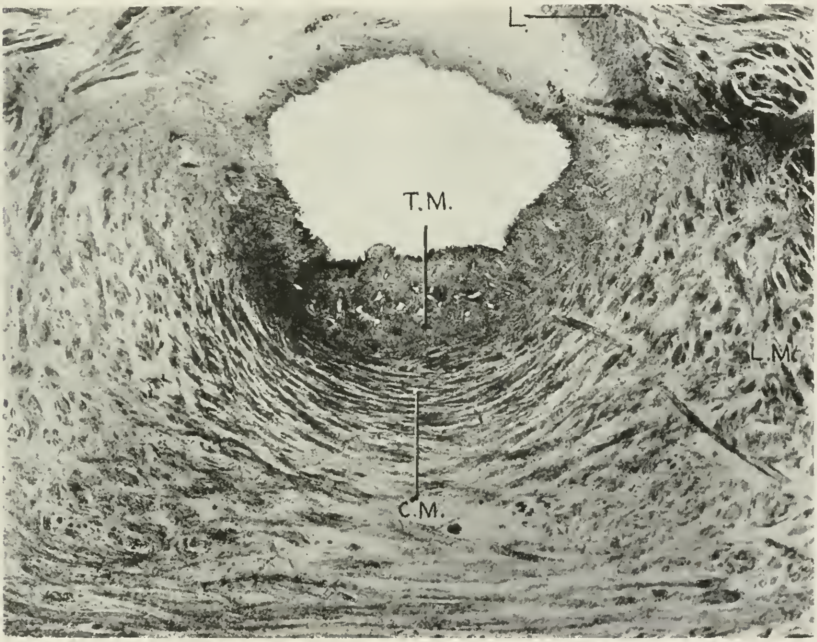


FIG. 11. CROSS SECTION OF A 276-MM. HUMAN EMBRYO THROUGH PROXIMAL PART OF VESICAL ORIFICE

The circular layer hugs the urethra but reaches only to the mid-lateral wall. In the submucosa are seen numerous lymph or vascular spaces and trigonal muscle fibers. The longitudinal bundles have begun to take on a transverse direction and are sweeping up over the urethra. The longitudinal fibers that flow along the roof of the urethra have appeared at this level. *L.M.*, longtitudinal muscle; *C.M.*, circular muscle; *T.M.*, trigonal muscle; *L.*, longitudinal muscle of roof of the urethra. Embryo, Carnegie Institute 2607, slide 44, section 2. × 25.

urethra, which has been invaded and distorted by prostatic tubules.

At a point opposite the mediolateral aspect of the vesical orifice, there may be found lying in close relationship to the fibers of the loop of the external longitudinal muscle, a few striated muscle fibers. These fibers are often quite close to the urethral mucosa and even lie between the prostatic tubules. As they pass downward and forward, they increase in number until at a point below

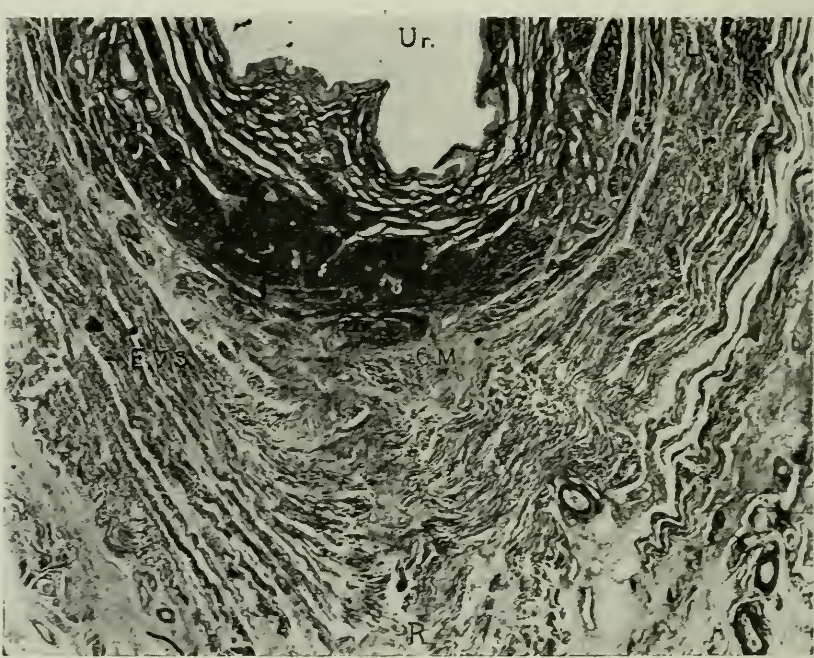


Fig. 12. Cross Section Through the Membranous Urethra of a Term Human Fetus

Shows the raphe formed by the striated fibers of the external vesical sphincter, which probably helps form the recto-urethralis muscle. *Ur.*, urethra; *E.V.S.*, external vesical sphincter; *C.M.*, circular muscle; *R.*, raphé; *L.*, longitudinal bundles. Embryo, Carnegie Institute 2679, slide 35, row 1, section 3. × 25.

the lower border of the loop where it passes in front of the urethra, they pass across the midline and form a sheath of striated fibers running in a direction generally circular as regards the urethra,

but extending only about half way around it. Following them downward, however, the fibers pass further and further dorsally until at a point opposite the apex of the prostate, they join those from the other side in a raphe, thus forming from this point downward a complete circular sheath about the urethra. This system of striated muscle makes up the external vesical sphincter. The fibers of this raphé pass downward to the rectum and form what is undoubtedly the recto-urethralis muscle (fig. 12).

The trigonal muscle, as has been described above, passes down over the posterior border of the vesical orifice and spreads out as an internal longitudinal layer over the posterior aspect of the urethra. The fibers pass between the openings of the prostatic ducts, ejaculatory ducts and prostatic utricle, and continue on down for some distance past the verumontanum. Some fibers may be traced as far as the beginning of the membranous urethra.

PHYSIOLOGY OF MICTURITION

According to Fearnsides (32) the bladder is supplied by two sets of efferent nerves, the first from the lowest thoracic and upper lumbar nerve roots by way of the white rami communicantes, and the lumbar or inferior splanchnic nerves to the inferior mesenteric ganglia, and finally by way of the hypogastric nerves to the hypogastric plexus and the bladder. The second set originates in the roots of the sacral nerves and passes downward in two branches, the nervi erigentes or pelvic nerves comprising the vesical part of the hypogastric plexus, and so supplies the unstriped muscle of the bladder, the urethra and corpora cavernosa; while the two pudic nerves form the motor path to the striped voluntary muscle of the urethra. Little is known accurately as to the exact anatomical course of the tracts within the central nervous system which carry impulses concerned with voluntary control of micturition. Valentine in 1839 proved that excitation of certain portions of the brain, especially the cerebral peduncles, the corpora striata and the optic thalmus instigate movements of the bladder, and Czyblarz and Marbury (33) described a cortical bladder center in the

Rolandic motor area. Pathologico-clinical investigation suggests that the path of the impulses lies in the posterior portion of the lateral columns of the spinal cord near to the pyramidal tract. Stewart (34) found that the physiological innervation of the bladder differs from animal to animal as does the anatomy. Elliott (35) confirming the work of Sokownin (36) and Zeissl (37), found that stimulation of the peripheral cut end of the hypogastrics in the dog caused contraction of the urethra and trigone, and stimulation of the pelvics caused relaxation. He denervated a cat's bladder and the operation did not interfere with micturition. He believes the trigone functions as an inhibitor to the detrusor of the bladder. Barrington (38), confirming Stewart's work, found that division of the hypogastrics produced a persistent contraction of the bladder with a heightening of tone and loss of autonomic reflex. Division of the pelvic nerves resulted in a marked bladder palsy. Division of the pudics caused incontinence in the cat. Stewart, Barrington, Guyon (39), Langley and Anderson (40) are at some variance in details but agree in general that sectioning of the hypogastric nerves causes no interference with the micturition reflex. Griffith found that although the bladder is a median unpaired organ, yet each half may contract independently, and there is no tendency for contractions to spread over the midline along direct continuity of muscle fibers. The nerves are bilateral and both sides must be stimulated simultaneously to obtain uniform contractions. The contractions are not confined to one muscular layer but include both.

Since, according to pharmacological studies, it has been shown that much information concerning the innervation of smooth muscle can be gained by tests with various drugs, pieces of trigonal muscle and of the fundus of the bladder were obtained from the operating room for this purpose. The tissue was preserved in Locke's solution and was tested for nerve reactions by Dr. D. I. Macht in the Pharmacological Laboratory. The trigonal muscle contracted on treatment with epinephrin and also responded to the action of ergotoxine. Inasmuch as epinephrin and ergotoxine are the two most important drugs, which act upon the *true*

sympathetic nerve endings, this response points to the trigone being innervated by true sympathetic fibers. He further tested the tissue in regard to its response to pilocarpin, physostigmin and atropine, and found that none of these drugs produced any contraction or relaxation of the trigonal muscle. Pilocarpin and physostigmin are the chief representatives of the so-called pressor drugs, which stimulate the parasympathetic nerve endings, while atropine is the chief paralysant drug belonging to this group. Failure of the trigone to respond to these drugs would, therefore, seem to indicate that the trigone is devoid of parasympathetic nerve terminals. Experiments upon the trigonal muscle with nicotine gave a response indicating the presence of ganglionic structures in that layer. The fundus gave reactions for both sympathetic and parasympathetic nerves. A dog's trigone gave the same reactions, but experiments on the fundus of the rat's bladder showed marked response to both pilocarpin and atropine, showing that this muscle does have parasympathetic terminals.

A cystoscopic study of the mechanism of urination was made upon a series of fifty patients. With the cystoscope in position, the bladder was filled to capacity with water and the patient alternately urged to strain and then to relax. While the patient is straining, an indirect cystoscope can be drawn into the posterior urethra just as in a tabetic bladder. The vesical orifice, when dilated while making an attempt to void, is not circular but is pear-shaped, the small part being dorsal. This shape is undoubtedly due to the contraction of the trigonal muscle and the synchronous relaxation of the two loops of muscle about the vesical orifice. The movement is small and slow on the ventral aspect as the orifice dilates, but on the dorsal side the trigonal muscle accelerates and augments the relaxation of the small loop. The contraction of the trigonal muscle is powerful as shown by the depression of the floor of the urethral orifice and the marked upward movement of the verumontanum. The striae anterior to the verumontanum are apparently fixed at the lower ends, but the verumontanum moves upward with straining, and in some cases appears to enter the bladder proper. The plica ureterica remains approximately fixed throughout.

DISCUSSION

It is felt that one cannot propound, even with the present increase in our anatomical data, a complete theory to account for the phenomena of micturition. There is too great a deficiency in our knowledge of the mechanics of muscular structures which do not have bony attachments, simple circular sphincters excepted. The points brought out in this paper, therefore, are presented without the accompaniment of any such theory. It is clear that at the vesical orifice we are not dealing with a simple sphincter. The muscle fibers comprising the loops about the upper end of the urethra, arise from and are closely connected with the longitudinal coat of the bladder, but we do not know whether they contract in unison with it or not. The trigonal muscle exerts its pull in the direction of the open part of this muscular loop, and there is nothing in the present studies to indicate that it may not, as has been suggested, act to pull open or elongate the vesical orifice. Pharmacological and embryological studies show, by demonstrating for this muscle an origin and a nervous control different from those for the rest of the bladder, that it is quite reasonable to suppose that its contraction and relaxation occur independently of those of the rest of the bladder.

Muscular structures about the neck of the bladder never hitherto accurately known have been described. To avoid confusion, descriptive designations have been employed throughout the paper, but at this point new names are proposed: for the outer loop about the vesical neck, arising from the external longitudinal muscular layer of the bladder, the external arcuate muscle of the vesical orifice (musculus arcuatus externus orificae vesicalis), and for the inner loop arising from the internal circular muscular layer of the bladder, the internal arcuate muscle of the vesical orifice (musculus arcuatus internus orificiae vesicalis).

I desire to express my thanks to Dr. Hugh H. Young for suggesting this problem and for his many kindnesses and keen interest throughout the work; to Dr. Geo. L. Streeter for putting at my disposal the collection of the Carnegie Institute of Embry-

ology, as well as for his many helpful suggestions and also for the material assistance rendered by his staff in the preparation of the specimens and the photomicrographs; and to Dr. D. M. Davis for his interest throughout the study.

SUMMARY

1. Embryologically, the trigonal muscle is of mesodermal, while the fundus is of ectodermal origin.

2. The following new embryological data are presented: in an embryo of 3.5 mm., the primary excretory duct has reached the cloaca as a patent tube with a blind end; at 3.9 mm., it enters the cloaca. The ureteral bud appears at 6 mm., and at 9 mm., the bud which started to grow laterally, has turned and is growing cranially, and at 10 mm., it has reached the mesonephros, the common duct has been incorporated in the bladder, and the Wolffian ducts and ureters meet at the bladder wall. In a 13 mm. embryo, the cranio-lateral migration of the ureters has begun; and at 21 mm., the triangle formed by connecting the ureteric openings with Müllers hillock (the openings of the Wolffian ducts) is an equilateral triangle. At this stage, the separation of the bladder from the urethra has begun, and the muscles have begun to develop in the trigone. The ureters in small embryos commonly enter the bladder on the dorsal side in a perpendicular direction, but at 80 mm. have acquired an oblique course.

3. The trigonal muscle is a definite entity arising from the longitudinal muscle fibers of the ureters, and is superimposed upon the muscles of the bladder wall.

4. The trigonal muscle plays an active part in the process of micturition, pulling open mechanically the internal vesical orifice.

5. There is more elastic tissue in the trigone than elsewhere in the bladder.

6. According to pharmacological tests, nerve ganglia and true sympathetic fibers are present in the trigonal muscle while the fundus of the bladder has both sympathetic and parasympathetic fibers.

7. The internal sphincter is a surgical designation and not an anatomical entity, the vesical orifice being closed by two loops or arcs, one arising from the internal circular layer and the other from the external longitudinal layer of the bladder wall. New names for these structures have been proposed.

8. The external sphincter is made up of striated fibers which have their origin in the lateral wall of the prostate near the vesical orifice. These fibers do not make a complete circle of the urethra but end in a raphé of connective tissue behind the membranous urethra.

9. The prostatic tubules invade the internal circular layer of the posterior urethra and probably minimize its value as a sphincter muscle.

REFERENCES

(1) Bell, Sir Charles: Med.-Chir. Tr. Lond., 1812, iii, 171.
(2) Ellis, G. V.: Med-Chir. Tr. Lond., 1856, xxxix, 327.
(3) Walker, J. W. Thompson: J. Anat. & Physiol., 1906, xl, 189.
(4) Kalischer: Die Urogenital-muskulatur des Dammes. Berlin, 1900.
(5) Frisch and Zuckerkandl: Handb. d. Urol. Wien., 1903, 1, xxiii.
(6) Griffith, Joseph: J. Anat. & Physiol., 1891, xxv, 549.
(7) Quain: Anatomy, iii, pt. iv, p. 206.
(8) Metzner: Nagel Handb. der Physiol. d. Menschen. Berlin, 1907, 300.
(9) Kohlrausch: Zur Anat. u. Physiol. der Beckensorgane. Leipzig, 1854.
(10) Versari, R.: Ricerche n. lab. di anat. norm. d. r. Univ. di Roma, 1907–1908, xii, 5–59.
(11) Versari, R.: Ann. d. mal. d. Org. genito-urin. Par., 1897, xv, 1089.
(12) Zuckerkandl: Nothnagel Spec. Path. u. Therapie, xix, I–II.
(13) Kelly and Burnam: Diseases of the Kidney, Ureter and Bladder, 1914, I–II, 198.
(14) Griffith, Joseph: J. Ant. & Physiol., 1894–1895, xxix, pp. 61, 264.
(15) Eteau: Ann. d. mal. d. Org. genito-urin. Par., 1905, xxii, 241.
(16) Schewkumuko, W. N.: J. d. urol. med. et chir. Par., 1912, i, 131.
(17) Testut, L.: Traite d. Anat. Humaine, iv, 460.
(18) Ramsey: Johns Hopkins Hosp. Bull., Balto, 1896, vii, 201.
(19) Cecil: Calif. State J. San Fran., 1915, xiii, 34.
(20) Mertz: Urol. & Cutzn. Rev. St. Louis, 1918, xxii, 533.
(21) Delbet, Poirier and Charpy: Traite d. Anatomie Humaine, v, 110.
(22) Young, H. H.: Surg. Gynu. & Obst., Chicago, June, 1918, xxvi, 608.
(23) Mall, F. P.: Johns Hopkins Hosp. Rep. Balto., 1896, i, 171.
(24) Treves: Applied Anatomy. 7th ed., 477.
(25) Waldeyer, W.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturu. Cl. Berlin, 1897, 732.

(26) Waldeyer, W.: Anat. Anz. Jena, 1892, 259.
(27) Satani, Y.: J. Urol. Balto., 1919, iii, 247.
(28) Felix, W., Keibel and Mall: Human Embryol., Phila. and Lond., xix, 752.
(29) Lowsley, O.: Am. J. Anat. Balto., 1912, xiii, 299.
(30) Watson, E. M.: Am. J. Anat. Balto., 1918, xxiv, 398.
(31) Howell: Text Book of Physiology. 6th Ed., p. 857.
(32) Fearnsides, E. G.: Brain. 1918, xl, 149.
(33) Czyblarz and Marburg: Jahrb. f. Psychiat. u. Neurol., Leipz. and Wien, 1901, xx, 134.
(34) Stewart: Am. J. of Physiol. Balto, 1899, ii, 189.
(35) Elliott: J. Physiol. London, 1907, xxxv, 367.
(36) Sokownin: Arch. f. d. ges. Physiol. 1874, viii, 600.
(37) Zeissl: Arch. f. d. ges. Physiol. Bonn, 1893, liii, 560.
(38) Barrington, F. J. P.: J. Exper. Physiol. Lond., 1915, viii, 33.
(39) Guyon. Ann. d. mal. d. org. genito-urin. Paris, 1894, xii, 561.
(40) Langley and Anderson: Am. J. Physiol. Boston, 1895, xix, 67.

The following references were also consulted:

Disse, J.: Handb. d. Anat. d. Mensch. Jena, 1902, vii, I, 1.
Heymann, A.: Centralbl. f. d. Krankh. d. Harn-w. Sex-Org. Leipz., 1906, xvii, 177.
Heymann, A.: Centralbl. f. d. Krankh. d. Harn-w. Sex-Org. Leipz., 1905, xiv.
Young and Cecil: Tr. Am. Urol. Ass. Brookline, 1917, xi, 124.
Fuller: Am. J. M. Sc. Phila., 1897, cxiv, 440.
Quinby: Cabot's Modern Urology. 1918, i, 551.
Morris: Anatomy. 1893, p. 1035.
McCarthy: Med. Rec., 1918, xciv, 609.
Garceau and Kelly: Surg. Gynec. & Obst. Chicago, 1912, xv, 167.
Lowsley, O.: Surg. Gynu. & Obst. Chicago, 1915, xx, 183.
Young, H. H.: Ann. Surg. Phila., 1903, xxxvii, 668.
Young, H. H.: Johns Hopkins Hosp. Bull. Balto, 1898, ix, 100.
Cecil, A. B.: J. Am. M. Ass. Chicago, 1915, lxv, 1430.
Rieffel, H., and Descomps, P.: Encyclopedie Française d'Urologie, Par., 1904, i, 527.
Keyes: Urology. N. Y. and Lond., 1919, 475.
Young, H. H.: Johns Hopkins Hosp. Rep. Balto., 1906, xiii, 324.
Cathelin, F.: Urol. & Cutan. Rev. St. Louis, 1919, xxiii, 403.
Young, H. H.: Mem. & Bul. Int. Ass. of Urol., London, 1911, 116.
Jones, F. Wood: Anat. and Physiol, xxxvi, 1901, li.
Whiteside, Geo. S.: Med. Sentinel. Portland, Ore., xii, 1904, 553.
Krogius, A.: Urol. and Cutan. Rev. St. Louis, 1917, xxi, 606.

PLATE 1

Normal Bladder of Nineteen-Year Old Male

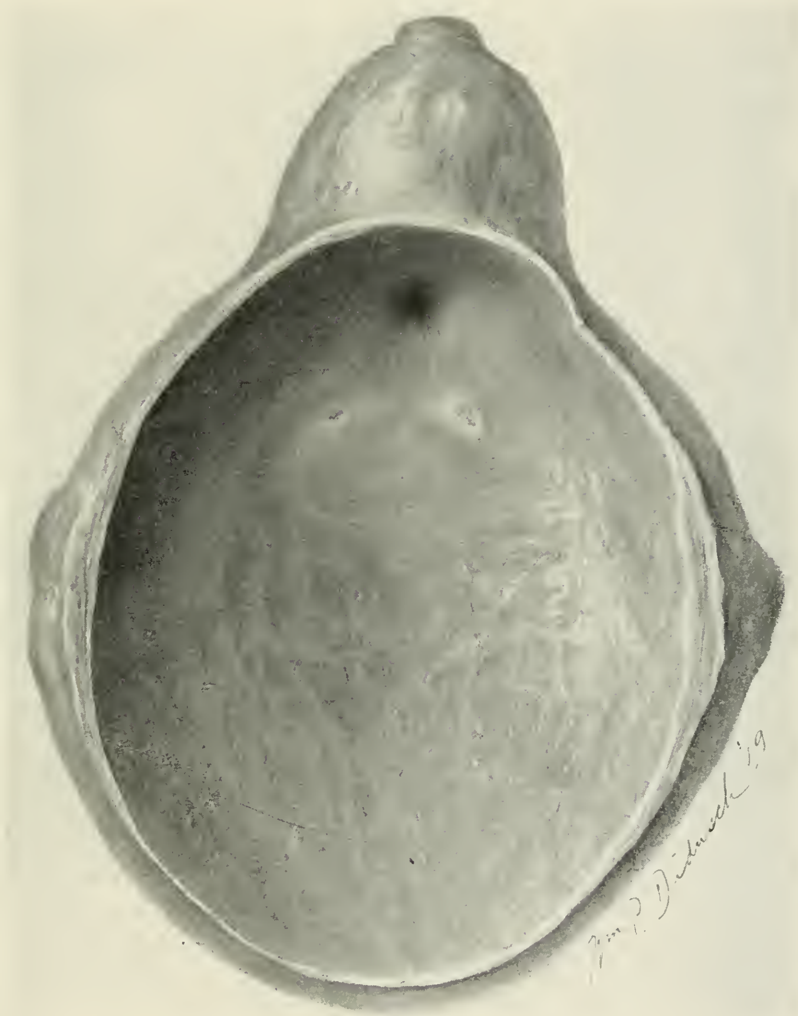


PLATE 2

A. Bladder of Nine Months Female

B. Bladder of Four Months Male

A

B

PLATE 3

1. A normal trigone. *2*. The trigonal muscle is raised exposing the circular muscle layer. *3*. The left ureter is dissected free from the bladder wall and the trigonal muscle pulled up as a sheet. The line of cleavage is marked by a layer of blood vessels. The external longitudinal layer of muscle is exposed by lifting the circular layer. *V.*, vesical orifice, *U* , ureter; *Ur.*, ureteral orifice; *T.M.*, trigonal muscle; *C.M.*, circular muscle; *L.M.*, longitudinal muscle; *X*, opening from which ureter was removed.

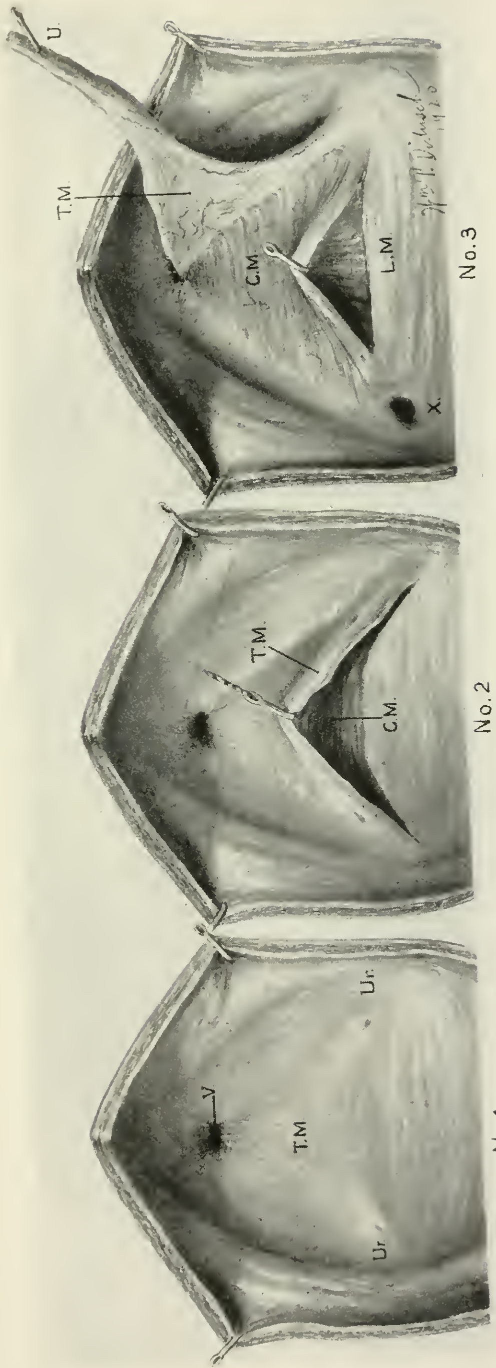
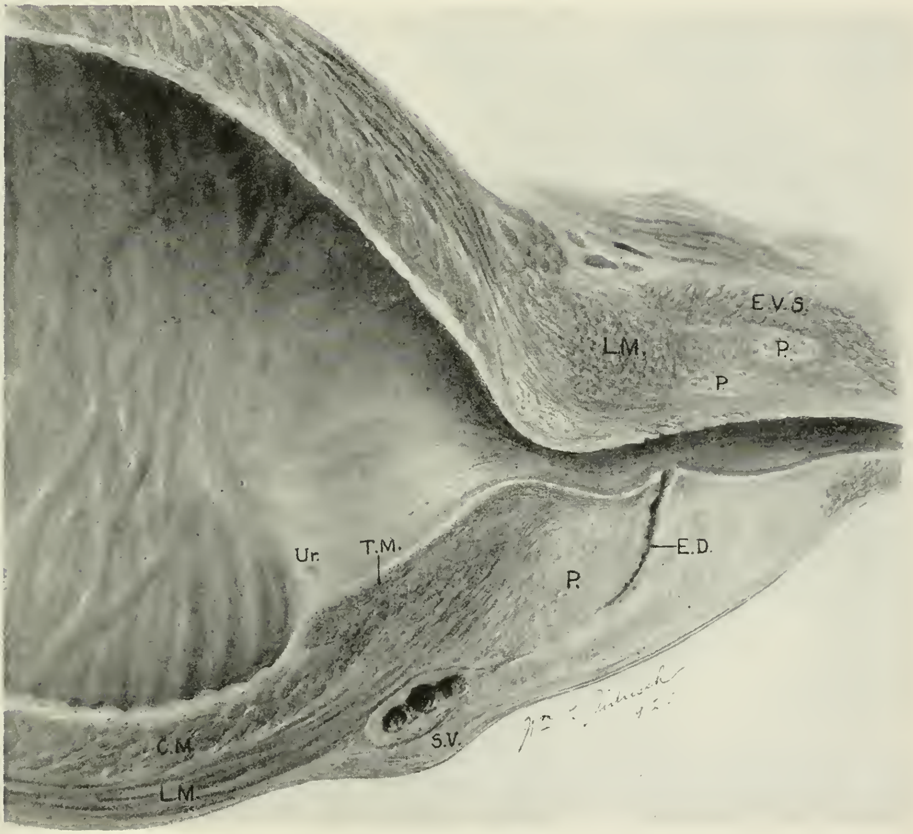

U.
T.M.
C.M.
L.M.
X.
No. 3
T.M.
C.M.
No. 2
V.
T.M.
Ur.
Ur.
No. 1

PLATE 4

Sagittal Section of Bladder of Adult


E.V.S.
L.M.
P.
P.
P.
Ur.
T.M.
E.D.
C.M.
L.M.
S.V.

TREATMENT OF ESSENTIAL RENAL HEMATURIA BY INTRAPELVIC INJECTIONS OF SILVER NITRATE

A. G. RYTINA

Baltimore

Hematuria is probably the most important sign and symptom in urology. It is due to a large number of different causes, the most common of which are neoplasm, tuberculosis and stone. It must always be regarded with deep concern and every aid known to urology must be employed in order to fathom it. Fortunately we have a series of diagnostic aids at our disposal which makes its diagnosis in the great majority of cases easy and certain. However cases arise which baffle the skill of the modern urologist, even though every diagnostic agent known to his specialty be employed.

There is a type of hematuria called by some for want of a better term essential hematuria which has certain very definite characteristics, viz, the bleeding is painless, more or less constant and more or less profuse. Negative findings are obtained, with the exception of blood in the urine, even though every clinical aid be employed, e.g., ureteral catheterization, functional tests, X-ray, pyelography, wax tip and urine culture. That such cases exist is undoubted, although the number of diagnoses as such will be smaller than actually recorded, because of our diagnostic limitations. For example, a beginning neoplasm of the kidney may give rise to hematuria which would be diagnosed as essential hematuria because the lesion is still so small that it would not be demonstrable, even though the X-ray, ureteral catheterization, functional tests, pyelography, urine culture, etc., were employed.

There are many theories advanced concerning the cause of these obscure renal hematurias, some maintaining that they are due to passive congestion (Randall (1)) Spitzer (2)) patchy

or diffuse fibrosis of the kidney (Payne (3)), the latter in association with the multiple microscopic calculi of the renal papillae, chronic papillitis (Braasch (4)), varicose papillae (Fenwick (5), Cabot (6), Braasch et al (7)), and nervous vaso-motor reflexes, without anatomic lesions of the organ (Carlo Santini (8). Marion (9) thinks it is due to glomerular nephritis, Billings (10) and Braasch (11) believe that infection by the bacillus coli communis may be the cause, while Ellsner (12) and others hold that it is the result of localized nephritis.

It is probable that all of the above mentioned causes may be found at various times to be provocative of hematuria, but that localized nephritis will be found more often than any other to be the cause of essential hematuria is the most commonly accepted theory. In this connection, it is also of interest to know that the hematuria may be nephritic in origin, even though the patient have no clinical symptoms of nephritis; that is, pathological examination of excised portions of the kidney may reveal nephritis and yet the patient show no albuminuria, casts, high blood pressure or retinal changes.

TREATMENT OF ESSENTIAL HEMATURIA

The treatment of essential hematuria may be divided into the conservative or non-operative and the radical or surgical.

Radical or surgical

Nephropexy. This treatment has been recommended but it is obvious that it has small chance of success and is only mentioned to be condemned.

Decapsulation. A number of cases have been reported in the literature, in which this method of treatment was productive of curative results. The probable explanation for the beneficial effect of this operation is the establishment of a collateral circulation after the decapsulation. However, Katzenstein's (12) experiments show that stripping of the capsule prevents rather than favors the formation of a new circulation.

Nephrotomy. This procedure is highly recommended by a number of authors. Payne and MacNider (13) extol this treatment most highly and report eight cases in which bisection of the kidney from pole to pole was curative in every case. On the other hand this method has failed in the hands of a number of different authors and the serious secondary bleeding reported by various operators necessitating nephrectomy makes this a method to be resorted to only in rare instances. In one of our cases mentioned below, nephrotomy proved valueless.

Nephrectomy. This method is of course too radical and is only to be considered as an emergency method. We should realize fully the possibility that the pathological cause of the bleeding may also be present in the other kidney, even though it is not itself bleeding. It is needless to mention that previous study must not only determine the presence of the other kidney but its normality in all respects must be proved.

Conservative or non-operative treatment

Any renal hematuria which has been thoroughly studied and found not to be due to stone, tuberculosis or neoplasm should first be subjected to the conservative method of treatment before considering surgical intervention. The various agencies employed for this purpose have been the internal administration of such drugs as lactates, ergot, etc., hypodermic administration of vaccines and the introduction into the circulation of horse and human serum and whole blood. Barringer (14) advises the use of serum both by subcutaneous injections and by direct topical application of the serum to the bleeding point in the kidney pelvis. Direct transfusion has also been tried (Allen (15)). Styptic injections into the kidney pelvis have been successfully employed by a number of different authors (Young (16), Kretschmer (17), Moore (18), Braasch (19).) Simple ureteral catheterization has been successful in stopping the bleeding in twenty-six cases of renal hematuria according to Braasch. Similarly, successful efforts have been reported by Braasch following the distension of the renal pelvis by methylene or colloidal silver

salts. Swartz (personal communication) had one case of renal hematuria to stop following an injection of thorium nitrate into the kidney pelvis.

Treatment by intra-pelvic injection of silver nitrate. The treatment of essential hematuria by intra-pelvic injections of 5 per cent silver nitrate solution is offered merely as an addition to our present armamentarium. It is not considered a specific for all these cases but is mentioned as a method that has been productive of good results, after many of the previously mentioned methods have failed to achieve the desired result. The technique is very simple and consists in the injection of 4 to 8 cc. of a 5 per cent solution of silver nitrate into the kidney pelvis, after a thorough urological examination has eliminated as far as possible the presence of stone, tumor, or tuberculosis from the bleeding side. The treatment is repeated in a few days if the desired result has not been achieved. The treatment is usually followed by some reaction, characterized by pain and increase in the hematuria.

As far as we are aware, Geraghty was the first to use this method of treatment for this type of hematuria. The explanation for its therapeutic virtue is unknown, unless it be the pronounced reaction that takes place in the kidney pelvis and kidney substance, as a result of this procedure. The hematuria may recur after a shorter or longer interval, necessitating a repetition of the silver injection.

In conclusion, I wish to cite in abstract three cases of hematuria in which this method was productive of fine results.

May 8, 1916. H. F. S. Married, age forty-four, physician. Complains of hematuria.

Family history. Negative.

Past history. Appendectomy five years ago. Had kidney colic at age of fifteen, and was told he had passed a stone. Has had no clots of blood in urine since that time. Had mumps ten years ago, complicated by orchitis. In November, 1915, he received a severe blow over the left kidney which was followed by the appearance of blood in the urine.

Present illness. Began passing blood in urine in December, 1915.

No pain except "daily aches" over the left kidney region. The urine clears up with rest in bed. The only symptom at present is hematuria.

Examination. External genitals normal. Urine is bloody and shows microscopically many red blood cells; no pus cells or bacteria. Rectal examination: Prostate and seminal vesicles negative.

Cystoscopy showed a normal bladder. Blood was seen issuing from the left ureter, clear urine from the right ureter. Ureteral catheterization of the right side showed a few epithelial and red blood cells, apparently due to trauma. From the left side were many red blood cells, no pus, no casts, and no organisms. Small ring of albumin in the urine from each kidney. Patient's phenolsulphonephthalein output was 60 per cent. The divided functional test showed a time of appearance on the left side of four minutes, on the right side five minutes. The output for the first half hour was 32 per cent from each side. X-ray of kidney and bladder negative. Pyelogram negative.

Diagnosis. Left essential renal hematuria. Following examination patient insisted on leaving hospital. He consulted an internist and from February 8, 1916, to June 8, 1916, he was given medical treatment, consisting of various sera, lactates, ergot, etc., without the slightest relief. On June 8, 1916, he again entered the hospital for the relief of hematuria, the findings being practically the same as on the first examination.

Treatment

June 10, 1916. Five cubic centimeters of 1 per cent silver nitrate were injected into the left kidney pelvis through the ureteral catheter without any effect on the bleeding.

June 21, 1916. Four cubic centimeters of 5 per cent silver nitrate solution were injected into the left kidney pelvis. Patient had severe pain following treatment and the hematuria was more severe for the next twenty-four hours.

June 22, 1916. Patient now passing perfectly clear urine. Microscopic examination showed no red blood cells.

June 1, 1916. Since treatment patient has gained 30 pounds in weight, feels fine, but has had one or two attacks of hematuria since treatment, which cleared up spontaneously. Microscopic examination of voided specimen shows only a few red blood cells, few pus cells, no organisms.

B. J. Age fifty-nine, widow. Complaint: Hematuria.

Family history. Negative.

Previous history. Six months ago had an attack of coma and was unconscious for several days; cause of coma unknown.

Present illness. Began about eight years ago when patient first noticed blood in urine. Bleeding was intermittent, sometimes lasting one day and at other times lasting a whole week. Lately has been profuse and persistent and gives patient much concern. Urinary examination: twenty-four hour output 1125 cc., specific gravity 1.022, albumin heavy ring, sugar negative, many red blood cells, no pus, no casts, no bacteria. Blood pressure 150 mm.

Cystoscopy. Cystoscopy showed a normal bladder. Ureteral catheterization: Urine from the right and left kidneys showed the same findings, namely, many red blood cells, no pus cells, no organisms, no casts, heavy ring of albumin. Six milligram of phenolsulphonephthalein were administered intravenously, appearing on the right side in twenty and on the left side in thirteen minutes. Output for the first half hour: right side, 20 per cent, left side, 28 per cent.

Diagnosis. Bilateral essential hematuria.

September 19, 1917. Ureteral catheterization gave the same results as on previous examination.

September 30, 1917. Ureteral catheterization: Eight cubic centimeters of 2 per cent silver nitrate were injected into the pelvis of each kidney without benefit.

November 2, 1917. Ureteral catheterization: Eight cubic centimeters of 2 per cent silver nitrate were injected into the pelvis of each kidney.

November 7, 1917. Ureteral catheterization: The urine was clear from left kidney and microscopically showed no red blood or pus cells. The urine from the right side was clearer than on previous examinations but still showed microscopically many red blood cells. Twelve cubic centimeters of 5 per cent silver nitrate were injected into the pelvis of the right kidney.

November 9, 1917. Urine perfectly clear but showed microscopically three or four red blood cells to the field and about the same number of white blood cells.

December 2, 1917. Letter from patient states that she is free from bleeding and feels quite well.

D. M. Age forty-nine, married, merchant. Complaint: Hematuria.

Family history. Negative.

Previous history. No history of renal colic.

Present illness. Patient noticed for the first time on February 14, 1918, that his urine was bloody. Had no other symptoms except a little frequency and burning.

Examination. External genitals normal. G1 and 2 very bloody. Rectal examination: Prostate and seminal vesicles negative. Cystoscopy showed a normal bladder. Blood was seen coming from the left ureter, clear urine from the right. Both ureters catheterized. Microscopic and chemical examination of urine from the right side negative. The urine from the left side shows the same findings as the bladder urine, namely, many red blood cells, no pus cells, no micro-organisms, no casts. Phenolsulphonephthalein was administered intravenously, appearing in five minutes from each side.

Diagnosis. Left essential renal hematuria. X-ray examination was made by Dr. Baetjer, who reported a definite shadow in the pelvis, which he thought was either a soft stone or collection of small stones.

Comment. From the history and symptoms of the case, as well as the urinary findings, the diagnosis of left essential renal hematuria was made, even though the X-ray diagnosis was stone in the pelvis. It was decided to subject patient to operation however, in the belief that even if the stone was not found, nephrotomy would achieve the desired result and cause cessation of the bleeding. Accordingly, on March 5, 1918, the left kidney was exposed, pyelotomy incision made, and a careful search for the stone carried out with negative results. Kidney was now split in two, the incision extending from pole to pole without finding any evidence of stone. Kidney was now sutured and the operation completed. Following operation, the patient's bleeding was worse than ever, and for several weeks he was given internal administration of lactates, ergot, etc., with negative results. Several intramuscular injections of horse serum proved likewise without avail. On May 28, 1918, 10 cc. of 5 per cent silver nitrate was injected into the kidney pelvis. Within forty-eight hours the bleeding had stopped entirely, and the urine was microscopically and chemically negative.

Patient seen on June 2, 1919. He had no symptoms or recurrences of the hematuria since June 1, 1918, the date of the cessation of the bleeding following the silver injection.

REFERENCES

(1) Randall: Jour. Amer. Med. Assoc., January 4, 1913.
(2) Spitzer: Jour. Amer. Med. Assoc., 1914, lxiii, 2110.
(3) Payne: Surg., Gyn., and Obs., July, 1916, pp. 76–79.
(4) Braasch: Trans. Sect. G. U. Dis., A. M. A., 1913, p. 41.
(5) Fenwick: British Med. Jour., 1900, p. 248.
(6) Cabot: Amer. Jour. Med. Soc., January, 1909.
(7) Braasch: See above.
(8) Carlo Santini: Sulle Ematuria considetre essenziali-Rivista Urol., 1911, No. 11.
(9) Marion: Hemorragies dans les néphrites et néphrites hématuriques. Le Progrés Med., 1911.
(10) Billings: Am. Jour. Med. Soc., 1910, p. 625.
(11) Braasch: Jour. Amer. Med. Assoc., September 20, 1913, p. 931.
(12) Ellsner: N. Y. State Jour. Med., 1913, xiii, 144.
Katzenstein: Ztschr. F. Exp. Path. u Therap., 1911, ix, 1.
(13) Payne and McNider: Jour. Amer. Med. Assoc., September 23, 1916, lxvii, 918–922.
(14) Barringer: Jour. Amer. Med. Assoc., October 26, 1913.
(15) Allen: Amer. Jour. Surg., December, 1913.
(16) Young: Jour. Amer. Med. Assoc., 1907, xlviii, 1654.
(17) Kretschmer: Surg., Gyn. and Obs., 1913, xvi, 34.
(18) Moore: Urol. and Cut. Rev. no. 8, 1913.
(19) Braasch: Trans. Sect. G. U. Dis., A. M. A., 1913, p. 41.

A NEW CULTURE METHOD FOR THE GONOCOCCUS

REPORT OF EXPERIMENTAL STUDIES[1]

ERNEST O. SWARTZ

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland, with the aid of funds granted by the United States Interdepartmental Social Hygiene Board for Research in the Prevention and Cure of Venereal Diseases

CULTURE METHODS FOR THE GONOCOCCUS

During our studies last year on the antiseptic action of Mercurochrome-220 (1) we were unable by means of laboratory experiment, to establish definitely its exact germicidal value against the gonococcus. This was due to our inability at that time to produce reliable, viable cultures of the gonococcus and to keep these cultures growing for any length of time. We were able to secure growth, but not of sufficient luxuriance to permit us to conduct germicidal tests. The importance of determining the germicidal value of Mercurochrome-220 as well as of the newer compounds which are being produced in the chemical laboratories of the Brady Institute, against the gonococcus—together with the fact that the question of new venereal prophylactics and treatment is being studied by us for the United States Interdepartmental Social Hygiene Board, led us to devote a large amount of work to the study of the cultural characteristics of the Diplococcus of Neisser. This is a prerequisite for the study of the germicidal action of drugs on the gonococcus in vitro.

Historical. Neisser (2) discovered and described the morphology of the gonococcus in 1879, but it was not successfully cultivated until six years later. In 1885, E. Bumm (3) first cultivated the gonococcus on solidified human placental serum.

[1] Part of this paper, giving details of method of gonococcus culture, was read before The Johns Hopkins Medical Society, April 19, 1920.

Since that time a large amount of work has been devoted to this organism.

Media. Upon review of the literature, one is impressed with the large number of special culture media which have been advocated from time to time. This, of itself, is an indication that the cultural difficulties are very great. Leading bacteriologists state that the gonococcus is delicate and very difficult to cultivate (4).

At least fifty media have been described (5). Each one, we are assured, will produce a luxuriant growth of gonococcus. These media vary markedly in composition and reaction, and many are very complicated and difficult to prepare.

Composition of media. It is generally agreed that the medium for successful gonococcus culture must be one very rich in protein, and that uncoagulated albumen derived either from human beings or animals is the most satisfactory protein for this purpose. Serum from man, from the horse, sheep, pig, goat and rabbit, has been used. Fluid obtained from hydroceles, from ascitic cases, from cases of hydro-thorax, and from ovarian cysts (6) has been used for protein enrichment of the medium. Sterilized mixtures of beer wort and albumen with or without the addition of horse serum (7), as well as protein derived from milk and eggs, have also been used for this purpose. The medium richest in protein content is not necessarily the best. Small amounts of human serum, heated to 57°C. favor the growth, while large amounts have a distinct bacteriocidal action on the gonococcus (8). In the course of these experiments, media was made containing hydrocele fluid in one instance, and containing ascitic fluid in another. There was no appreciable difference in the growth of gonococcus obtained upon the two media, even though ascitic fluid contained more than twice as much albumen as the hydrocele fluid. The occasional presence of bile in ascitic fluid did not have any appreciable effect on the growth of the gonococcus.

Recently, the presence of growth hormones or vitamins, a high concentration of free amino acids and a suitable hydrogen ion concentration, were declared to be the essentials of a medium for successful gonococcus culture. Following the work of Cole and Lloyd (9), and Stickel and Myer (10) along this line, we pre-

pared tryptamine media, according to their directions, with and without the addition of glucose. We did not have any better results with this medium than with the less complicated, more easily prepared media.

Reaction of media. Aside from the composition of the media, until quite recently, the reaction of the media was believed to be a factor of greatest importance, and stress was placed on the necessity of having the media of a definite degree of acidity. Authorities differed as to just what reaction produced the best results. Finger (11), and others in 1894, and Gurd (12) in 1908 advised a reaction frankly acid to litmus, while Vannod (13) used and advocated a medium alkaline to litmus, and always adjusted by titration the reaction of ascitic fluid used in his media. Hiss and Zinsser (4) in their latest edition, state that the most favorable reaction is neutrality or slight acidity. It was claimed by some authors that the value of the addition of human serum to media was due to the maintenance of the reaction of the media at or near neutrality by the serum, rather than to the supplying of additional protein. The addition of urine—which we did not find of any special value—probably produces the same result, the phosphates present acting as buffers, tending to maintain the reaction of the medium at a constant level.

In order to determine the optimum reaction for gonococcus culture media, a series of experiments was carried out. Slants of media titrated to a certain reaction of the hydrogen ion scale were made (14–15) (table 1). The media in these tubes had hydrogen ion concentrations ranging from pH 9.0 on the alkaline side, to pH 5.4 on the acid side. These tubes, planted with fresh viable gonococci, and stoppered so as to be air-tight, after lowering the oxygen tension, were incubated. This procedure was carried out on several occasions, using different strains of gonococcus. No growth occurred in tubes having an alkalinity of greater than pH 8.0, or an acidity greater than pH 6.6. A growth occurred on all media between pH 8.0 and pH 6.6 inclusive, the growth being most profuse on media near the point of neutrality. The point pH 6.6 is twenty times as acid as the most alkaline medium on which the gonococcus grew. These results indicate

that within the limits given, the reaction of the medium is not an important factor in the growth of the gonococcus, as it will grow luxuriantly on either alkaline or acid media if other conditions of growth are satisfactory.

The reaction of the media in these tubes was seen to change, and become less alkaline with the growth of the gonococcus on it. Inoculation of gonococci on slants of media, containing phenolsulphonephthalein as an indicator, was made. All strains of gonococcus with which we worked produced acid from our routine media to which no carbohydrate had been added, and which contained therefore only muscle carbohydrate. This was true whether liquid or solid media was used. Further studies on the

TABLE 1

Growth of the Gonococcus in media of varying hydrogen ion concentrations; reaction of culture media

	pH 5.4	pH 5.6	pH 6.0	pH 6.6	pH 7.0	pH 7.2	pH 7.4	pH 7.6	pH 7.8	pH 8.0	pH 8.6	pH 9.0
24-hour reading.........	0	0	0	+	+	+	+	+	+	+	0	0
48-hour reading.........	0	0	0	+	+	+	+	+	+	+	0	0
7th-day reinoculation...												
24-hour reading.........	0	0	0								0	0
48-hour reading.........	0	0	0								0	0

0 = No growth; + = growth of gonococcus; C = contamination.

production of acid by the gonococcus are being made, and will soon be reported.

When grown in liquid media, either beef or veal broth hydrocele media, the gonococcus fermented dextrose but failed to ferment maltose, levulose, saccharose, lactose and galactose; which is in accord with the findings of other investigators (8 and 31).

The fact that weak acids and alkalies inhibit the growth of the gonococcus on media immediately suggests the use as prophylactics of compounds containing either acid or alkali, which are odorless, colorless and non-staining, in strengths that are non-irritating to the urethral mucosa, and work along this line is being carried out in this laboratory, and will soon be reported.

Temperature. Our best results were obtained when the temperature of the incubator was maintained at or near 37.5°C.

Slight variations had no appreciable effect on the growth. Temperatures below 36°C. prolonged the time between the planting and the appearance of the growth. Temperatures of 40°C. or over killed the organism in a few hours. Boerner and Santos (16 and 17) state that a temperature of 43°C. kills the gonococcus in seventy-six minutes, 44°C. in fifty-four minutes, and 45°C. in thirty-seven minutes.

Oxygen tension. Martin (8) states that:

> The great variety in the composition of the media coupled with the very common experience that a medium successful in one person's hands, has not been equally so in others, suggests that either the individual strains of gonococcus vary much in their adaptability to a vegetative existence, or that some important factor is commonly overlooked in compounding of culture media.

We feel, as a result of this study, that a very important factor is usually overlooked, not in compounding the media, but in the method of growing the organism. This factor is the oxygen tension under which the organism is grown, although authorities (4 and 32) state that the gonococcus grows best in the presence of free oxygen.

Kruse (18) proved that oxygen tension has a very definite influence on the germination of microörganisms, and other investigators showed that the optimal conditions for growth of any single species do not depend so much on the presence or absence of oxygen as on its tension (19), and the term "microaerophile" (20) was applied to bacteria which thrive best at reduced oxygen tension. The principle of growing organisms at a reduced or partial oxygen tension is not new. To Wherry and Oliver (21) belongs the credit for discovering and calling attention to the fact that the gonococcus is a partial tension organism.

They modified somewhat the method of Nowak (22) and reduced the oxygen tension in the gonococcus culture tube by attaching to this tube, by means of rubber tubing, a freshly inoculated slant culture of B. subtilis. The B. subtilis tubes are changed daily. In its growth the B. subtilis uses up the oxygen and reduces the tension sufficiently to permit the gonococcus to grow,

as only a slight reduction of oxygen is essential. The same principle was applied in making growths on Petri dishes.

Other methods of reducing the oxygen tension in culture tubes have been suggested. Two years later, Chapin (23) advocated an atmosphere rich in CO_2 as facilitating greatly the primary cultivation of the gonococcus. He grew the gonococcus on a meat infusion urine agar in tubes placed under a bell jar, in which a lighted candle had been placed, and which was allowed to burn until there was not sufficient oxygen to support combustion. This gave an atmosphere rich in CO_2 and deficient in oxygen. He also produced his CO_2 in another series of experiments by the reaction of H_2SO_4 on sodium bicarbonate, and grew the gonococcus in an atmosphere of approximately 10 per cent CO_2. He concluded that his results were due to some modifications of the raw proteid of the media by CO_2 rather than to the reduced oxygen tension. Recently Maitra (24) reported very successful results in gonococcus cultures, by reducing the oxygen tension with CO_2 according to the method advocated by Chapin.

Last year, Ruedeger (25) published the results of experiments in which he produced luxuriant growths of gonococcus on certain media by tightly corking the culture tubes after inoculation. We did not use his media, but by simply sealing the tubes airtight as he suggested, we were able to secure heavier growths than when grown with an ordinary cotton plug in the tube. In the method we have used, we tightly corked the tube after removing a part of the oxygen contained therein.

Using the principle of reduced oxygen tension, produced however in a much simpler manner, the details of which will be given later, we have been able to grow very luxuriant gonococcus cultires on meat infusion hydrocele agar slants and on meat broth hydrocele media. The medium we used is but a slight modification of that used by Wertheim (26) in 1892 and a similar medium advocated by Young (27) in his work on gonococcus infections a few years ago.

Directions for making media. The media are prepared as follows:

1. Agar medium. Five hundred grams of fresh lean meat—veal or beef—is finely minced and thoroughly mixed with 1000 cc. of distilled water. This mixture is allowed to stand on ice for twenty-four hours. The liquor is then decanted and the remainder expressed through cloth, adding enough distilled water to make 1000 cc. Boil until the albumen of the meat infusion coagulates. Correct to an acidity of pH 7.6 by the use of $\frac{N}{10}$ NaOH. In order to eliminate the effect of CO_2 which is acid to phenolsulphonephthalein, media should be titrated at as nearly 100°C. as possible, for then in subsequent sterilizations the reaction will be less likely to be altered by driving off the CO_2 dissolved in the media. Boil again for a short time, filter and make up to 1000 cc. with distilled water. Add 10 grams Peptone Bacto.-Difco.), 5 grams NaCl (C. P.) and 15 grams agar, and boil until all is dissolved. If the media is to be used in hot climates or in the summer, 20 grams of agar should be used instead of 15 grams. This will give firm slants even after the addition of the hydrocele fluid. Let cool to 50°C. and then add the whites of three fresh eggs. Starting with a low flame, boil for ten minutes and again strain through cloth. Filter through a folded filter. This filtration is very slow, but can be hastened by placing flask and funnel in an autoclave at 10 pounds pressure. Place 5 to 6 cc. of the medium in each tube, and plug with cotton stopper. The test tubes best suited for this work measure about 150 mm. in length and about 16 mm. in diameter, and are made of heavy glass. Thin tubes are apt to crack when flamed and stoppered. These tubes are then autoclaved at 10 pounds pressure on three successive days. This sterilization changes the reaction from pH 7.6 to pH 7.4.

The hydrocele, ascitic or pleuritic fluid, having been collected under the most rigid aseptic surgical technique, is tested to insure its freedom from any bacterial organism. If sterile, it is kept in the refrigerator until needed. Uncontaminated hydrocele fluid is essential because of the great difficulty of sterilizing it if contaminated. Recently Grace (28) announced a method of autoclaving such fluids, but we have not made any media using fluid autoclaved in this manner.

Freshness of the fluid is not an essential, as we have had just as good results with fluid kept in the refrigerator for six months, as with the fluid a few hours old.

The tubes of agar are melted and placed on a water bath at about 50°C. To this melted agar is then added, hydrocele, ascitic or pleuritic fluid, in the proportions of 1 cc. of fluid to 2 cc. of agar. This proportion will permit the agar to harden into a firm slant and should produce about 0.5 cc. of water of condensation in the angle of the slant when the agar is firm. Tubes are then slanted or Petri dishes poured and allowed to harden.

The tubes are then stoppered so as to be air-tight, with sterile rubber stoppers and kept in the incubator to insure their sterility and to have the media warm when wanted for use. Undoubtedly some of our early failures at primary culture were due to the fact that we had not kept the medium warm, and had attempted to grow gonococcus on cold media. The gonococcus is very sensitive to changes in temperature, and material such as pus and urine, supposed to contain gonococcus, should not be allowed to cool. Cultures made from urethra or vagina should be kept at or near body temperature before being transferred to the incubator. The stoppering prevents evaporation and drying of the media. This is important as moisture is essential to the luxuriant growth of the gonococcus.

2. Liquid medium. If fluid media is desired, it is made exactly as above, except that the agar is omitted and after autoclaving, 1 cc. of a 10 per cent sterile solution of dextrose, maltose or whatever sugar is desired, is added.

The hydrocele, ascitic or pleuritic fluid is added in the same proportions as above. More can be used if desired, but 2 to 3 cc. per tube is sufficient to insure a good culture. These tubes are stoppered in the same manner as the agar slants, and kept in the incubator. This enables us to test the sterility of the medium as well as having it maintained at body temperature and ready for use at any time.

The stoppering of the tubes is quite important, as it prevents the drying out, hardening and cracking of the medium as well as the evaporation of the water of condensation. Also the num-

ber of contaminations is much smaller with the sterile rubber stoppers than when the ordinary cotton plugs are used.

Moisture. A series of experiments was carried out to determine whether moisture is essential to procuring a heavy gonococcus growth. Tubes of veal infusion hydrocele agar, stoppered with cotton plugs, were allowed to remain in the incubator at 37.5°C. for a week. At the end of this time, all the water of condensation had evaporated and the agar was cracking. A number of these were planted with fresh viable cultures of gonococcus and stoppered with rubber corks, (after the oxygen tension had been lowered) without the addition of any fluid to the tubes. To others of these tubes, 1 cc. of hydrocele fluid was added and it was flowed over the surface of the media. The tubes were then planted with the same gonococcus culture, the oxygen tension reduced and sealed. We obtained no growth on any of the dry tubes; but a heavy growth of gonococcus on each tube to which we had added hydrocele fluid. Later, hydrocele fluid was added to the tubes, on which no growth had appeared, and the second planting produced satisfactory gonococcus growth.

Recently, Kohman (33), working with the meningococcus grown under reduced oxygen tension, concluded that the "only advantage in growing the meningococcus with B. Subtilis in partial tension CO_2 comes from the increased moisture in the atmosphere and on the surface of the media under this condition." Experiments were carried out to determine if this held true for the gonococcus as well as for the meningococcus. A series of tubes were inoculated with fresh viable gonococcus and plugged with cotton stoppers. These were then placed in a desiccator in which there was an excess of moisture due to evaporation of water from saturated cotton sponges. The desiccator was then closed air-tight and placed in the incubator. Controls were made, using the same strain of gonococcus in the usual way, the oxygen tension reduced and the tubes stoppered. Heavy growth of gonococcus occurred on each tube with lowered oxygen tension in twenty-four hours. Two or three colonies appeared on the tubes in the desiccator in 48 hours, in which the oxygen tension had not been lowered, in spite of the excess of moisture

present. After forty-eight hours, several of these tubes were removed from the desiccator, the oxygen tension lowered and the tubes stoppered. In twenty-four hours, these tubes showed a profuse growth of gonococci. These experiments indicate that excess of moisture in the atmosphere alone does not account for the growth of gonococcus, but that reduced oxygen tension is essential for luxuriant growth.

In making primary cultures from the urethra in acute gonorrhea, this method has enabled us to grow the gonococcus from all cases showing organisms in smears and from a number in which the organisms could not be demonstrated microscopically. A pure culture can nearly always be obtained if great care is taken to cleanse the meatus and surrounding skin with alcohol and the culture material obtained on a platinum loop from some distance within the urethra. An occasional contamination with the staphylococcus or a diphtheroid bacillus occurs. The planting should be heavy, and care should be taken not to cut the surface of the media. We have never obtained a growth in the depths of a stab culture. We have found it of distinct advantage to inoculate the water of condensation in the angle as well as to stroke the slant and then gently flow the water of condensation over the surface of the slant.

Method of reducing the oxygen tension. We reduced the oxygen tension in a number of culture tubes by partially filling the tubes with CO_2 and then sealing tightly. The CO_2 used was ordinary commercial CO_2 supplied in cylinders for laboratory use. Satisfactory cultures were obtained by this means, but the percentage of contaminations was high, and this method was abandoned in favor of a less complicated method. As soon as the slant is inoculated, the oxygen tension in the tube is reduced by the following method which is new and, while of greatest simplicity, accomplishes the same results as the more complicated methods. The method is as follows: The tube held by the butt is rotated on its long axis so that the agar slant is uppermost and all the tube not in contact with agar is heated quite hot by passing through the Bunsen flame several times. Care must be taken not to kill the organisms on the slant by heat or crack the tube.

Passing through the flame three times is usually sufficient, and the tube is quickly stoppered with a sterile rubber stopper so as to be air-tight. The culture should be placed in the incubator before the tube cools.

The purpose of this procedure is to heat and drive out a part of the air from the tube, and the prompt sealing maintains this reduced tension in the tube. A little practice will enable one to reduce the oxygen in this manner without killing the organisms or cracking the tube. A slight coagulation of the albumen with consequent change of color, at the tip of the slant, indicates that the tube is heated sufficiently.

A series of tests were carried out with tubes so treated, and we found when measured by a special mercury manometer—constructed for this purpose—(see fig. 1), that, after the tube had cooled to 37.5°C., the atmospheric tension had been reduced from 70 to 100 mm. of mercury—a reduction of about 10 per cent. The amount of reduction varies with the size of the tube and the temperature to which it is heated.

Description of manometer used to measure oxygen tension in culture tubes (fig. 1, A, B, and C). This consisted of two glass tubes about the size of culture tubes, connected with each other by means of heavy rubber tubing, in such a way as to be air-tight. This U-shaped apparatus is partially filled with mercury and held in a stand in such a way that the two glass tubes are vertical and parallel. The smaller tube is corked with a perforated rubber stopper through which there protrudes one arm of an inverted U made of glass tubing. The other arm of this glass U perforates a rubber stopper used to stopper the culture tube. The reduction of oxygen in the culture tube draws the mercury up in the short arm of the manometer as the culture tube cools. Measurement of the amount of movement of this mercury column in millimeters gives an index of the reduction of oxygen in the culture tube. In reading the mercury movement, it is necessary to lower the long arm of the manometer sufficiently to depress the mercury in the short arm to the level at which it stood before the culture tube was attached. This is shown in figure 1: A showing mercury level in two tubes of manometer;

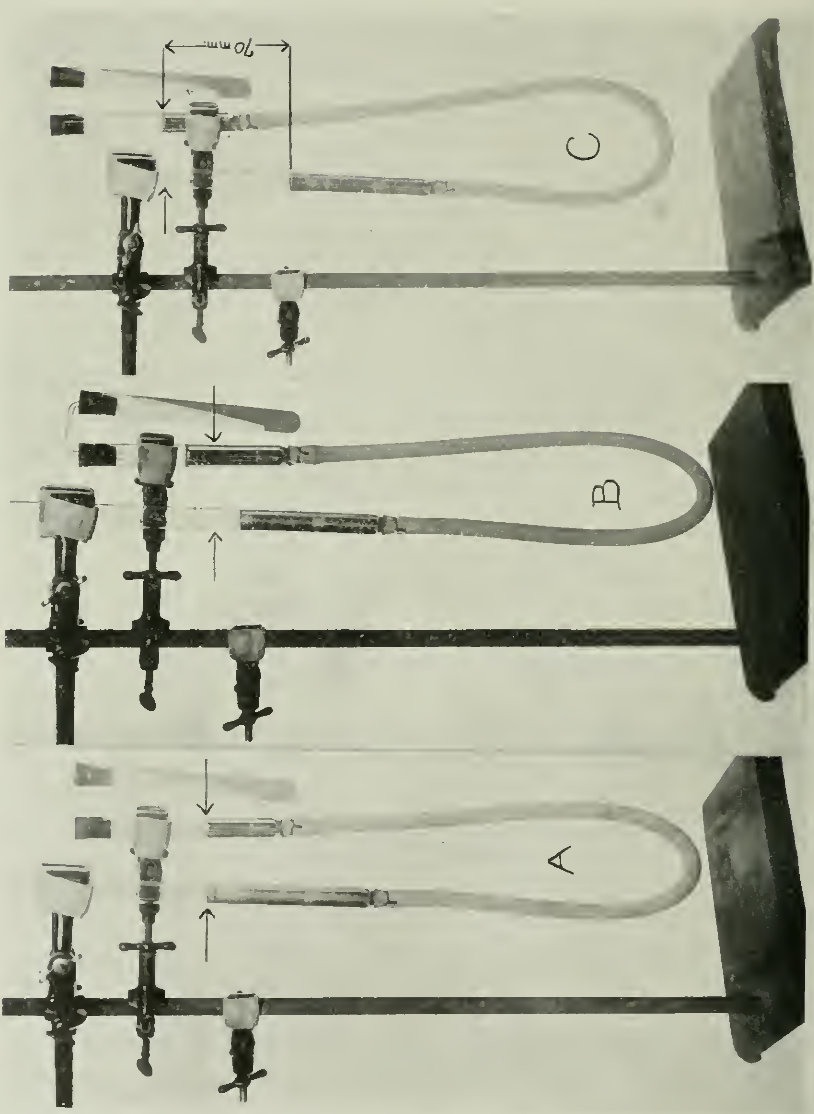


Fig. 1

B showing mercury rising in short tube; *C* showing mercury in short tube after mercury in long arm has been lowered to the level maintained in *A*. The difference in mercury level in the two tubes shows the reduction of atmospheric pressure in the culture tube, as expressed in millimeters of mercury.

This simple method of reducing the atmospheric tension in culture tubes has been used for the past six months in our laboratories with excellent results, and we have produced several thousand very luxuriant growths of gonococcus in this manner.

The same principle was applied to growths on plates. Instead of making tube slants, the media was poured into Petri dishes. Strokes grown at ordinary atmospheric oxygen tension gave no growth or an occasional very scanty one (fig. 2, *A*). The same strain of gonococcus grown on the same medium gave a profuse growth when grown in a desiccator, from which 10 to 25 per cent of the air had been exhausted by a suction pump (fig. 2, *B*). This method does away with the necessity of maintaining fresh cultures of B. subtilis or other organisms to be used in the reduction of the oxygen tension as advocated by Wherry and Oliver (21), Nowak (22), Theobald Smith (29), and others. It also eliminates the use of CO_2 in culture tubes and plates (23) (24) and the necessity of sealing Petri dishes with plasticine or adhesive (30).

The value of this method is emphasized by the fact that we have produced rich gonococcus growth on even plain agar, plain beef and veal infusion agar, without the addition of hydrocele, ascitic fluid or blood serum. A heavier growth, however, was always produced when the hydrocele or ascitic fluid was added to the agar. At least a dozen different strains of gonococcus gave these results. With but one exception, we have failed in every instance in our attempts to get a rich heavy growth of gonococcus on any of these media, when we did not reduce the oxygen tension. One strain of gonococcus, after many subcultures, gave a scanty growth on plain agar in a cotton stoppered tube. We were not able to secure a subculture from this one tube. We did not find any great difference in ease of cultivation or in the luxuriance of the growth of the different strains. We

Fig. 2

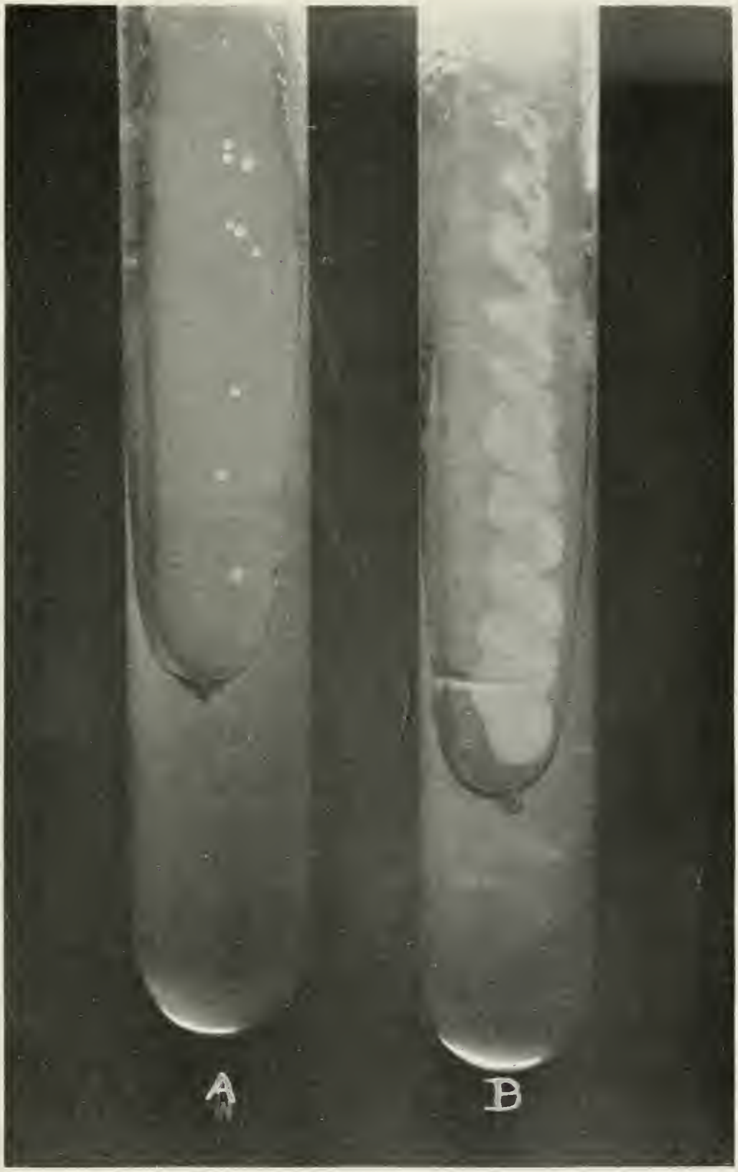


Fig. 3

have not as yet been able to produce a luxuriant primary growth on plain unenriched agar by any means. Luxuriant growth on media to which hydrocele fluid was not added, has only been obtained from a strain of organisms that have been subcultured a number of times. We have a number of times been surprised to find no growth or a very scanty one on slants in a series, and a search for the cause revealed a cracked test tube (A) due to overheating, the crack having admitted the air (fig. 3).

Description of colonies. On slants, the colonies begin to appear in fifteen to eighteen hours (fig. 4, *B*) as small translucent points. In twenty-four to thirty hours, the growth even in primary cultures (fig. 5, *A* and *B*) is usually very heavy. The colonies appear as delicate grayish moist-looking translucent spots which tend to remain discrete for a few days. Individual colonies are circular, with scalloped margins, sometimes slightly raised, and delicate radial striations. The centers are granular and viewed by transmitted light have a brownish hue, and occasionally a yellow tinge. The growth appears slimy, but is easily removed from the slant by washing with normal salt solution and makes a flaky emulsion.

The growth does not appear as quickly in the liquid media as on the slants, requiring forty-eight to seventy-two hours. The growth is never as heavy in the liquid and appears as a delicate film on the surface, with or without tiny strings hanging from its under surface. As the culture ages, some of the organisms sink to the bottom. The fluid medium is never clouded by the gonococcus. If a contamination is present, the medium becomes cloudy.

The viability of the gonococcus on this medium is about 7 days, and subcultures should be made every few days. We have been able to secure growth on several occasions from ten-day old cultures.

We have not seen any gonococci in our work which were not Gram-negative. All the strains with which we worked fermented glucose, but failed to ferment maltose, levulose, saccharose, lactose and galactose and failed to grow on ordinary media, with but one exception. Involution forms were rare in primary cul-

tures, but appeared after two or three subcultures. After a strain had been subcultured for several weeks, occasionally the

Fig. 4

growths would not be profuse. A transfer from solid to liquid media for several generations usually restored the luxuriant growth.

Fig. 5

CONCLUSIONS

1. The presence of reduced oxygen tension is essential to the profuse growth of the gonococcus. A reduction of 10 per cent of normal atmospheric pressure is sufficient.

2. The medium giving the most luxuriant growth is one rich in human proteid.

3. Moisture is essential for the growth of the gonococcus.

4. A luxuriant growth of gonococcus can be obtained on media, the reaction of which varies between pH 6.6 in the acid range and pH 8.0 in the alkaline range, of the hydrogen ion scale, if grown in partial oxygen tension.

The following have been described.

5. A simple, easily prepared medium which has been proven to be satisfactory for the primary culture and growth of the gonococcus.

6. An extremely simple, reliable method of reducing the oxygen tension in culture tubes.

Note: I desire to express my indebtedness to Dr. David M. Davis for suggestions and assistance throughout the work; to Dr. C. L. Deming for assistance during the early part of the culture experiments; to Dr. A. T. Shohl for his coöperation in the determinations of hydrogen-ion concentration; and to Dr. Hugh H. Young, the Director of the Brady Institute, for his constant encouragement.

REFERENCES

(1) Young, H. H., White, E. C., and Swartz, E. O.: A new germicide for use in the genito-urinary tract: "Mercurochrome-220." Jour. Amer. Med. Assn., November 15, 1919, lxxiii, 1483–1491.

(2) Neisser, A.: Cent. f. d. Med. Wissenschaft., 1879, 17–497.

(3) Bumm, E.: (1) Menschliches Blutserum als Nährboden für pathogene Mikro-organismen. Deutsche Med. Wchnschr., Leipzig, 1885, No. 53, p. 910.

(2) Beitr. z. Kenntnis des Gonococcus. Deutsche Med. Wochnschr., Weisbaden, 1885, 11–508.

(4) Hiss and Zinsser: A Text Book of Bacteriology. 4th Edition, 1919, pp. 381.

(5) Watabiki, Tomomitsu: Culture media for the gonococcus. Jour. of Inf. Dis., 1916, xix, 733.

(6) McCann: Fluid in ovarian cysts as a medium for the cultivation of the gonococcus and other micro-organisms. Lancet, 1896, 1–149.

(7) Lumiere and Chevrotier: (1) Sur nu nouveau milieu de culture eminemment propre au developpement du gonocoque. Compt. rend. Acad. d. Scienc., 1913, 157–1097.

(2) Sur la Resistance du Gonocoque aux basses temperatures. Compt. rend. Acad. d. Scienc., 1914, 139–158.

(8) Martin, W. B. M.: The isolation of the gonoccocus and its differentiation from allied organisms. Jour. Path. and Bacteriol., 1911, xv, 76.

(9) Cole, I. W., and Lloyd, D. J.: The preparation of solid and liquid media for the cultivation of the gonococcus. Jour. Path. and Bacteriol., 1916–1917, xxi, 267.

(10) Stickel, J. E., and Meyer, K. L.: Peptic and triptic digestion products as inexpensive culture media for the routine bacteriological work. Jour. Inf. Dis., 1918, xxiii, 68.

(11) Finger, Ghon, and Schlagenhaufer: Beitr. z. Biol. des Gonococcus. Arch. f. Dermat. u. Syph. Wien, 1894, xvi, 203.

(12) Gurd, F. B.: A contribution to the bacteriology of the female genital tract, with special reference to the detection of the gonococcus. Jour. Med. Res., Boston, 1908, xviii, 291.

(13) Vannod, Th.: (1) L'agar Ordinaire, comme milieu de cultur du Gonocoque. Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1905, Abth. I, Orig., Bd. xl, S. 162.

(2) Contributions a l'etude du Gonocoque. Ibid., 1907. Abth. I, Orig., Bd. xliv, S. 10.

(14) Clark, W. M.: The reaction of bacteriologic culture media. Jour. Inf. Dis., 1915, xvii, 109.

(15) Clark, W. M., and Lubs, H. A.: The colorimetric determination of hydrogen ion concentration and its application in bacteriology. Jour. Bacteriol., 1917, ii, 1–34.

(16) Boerner and Santos: Med. Klinik, 6:21, 1914, x, 1062.

(17) Pederson, V. C.: A Text Book of Urology. 1919, p. 502.

(18) Kruse: Allgemeine Mikrobiologie, 1910.

(19) (a) Porodko: Studien über den Einflub. der Sauerstoffspannung auf pflanzliche Mikro-organismen. Pringsheim Jahrb. f. Wissenschaft. Botanik. Jahrg., xli, 1905, Heft I.

(b) Chudjakow: Zur Lehre von der Anaerdliose. Teil I, Moskow, 1896. Ref. Centralbl. f. Bak. Abt., II, 1898, 399.

(c) Winogradsky: Recherches sur l'assimilation de l'zaote libre de l'atmosphere par les microbes. (Extract des Archives des Sciences Biologiques, III, 1895. No. 4, Petersbourg.)

(20) Bierjerinck: Centralbl. f. Bakteriol., 1893, xiv, 827.

(21) Wherry, W. B., and Oliver, Wade W.: Adaptation of certain tensions of oxygen as shown by gonococcus and other parasitic and saprophytic bacteria. Jour. Inf. Dis., 1916, xix, 288.

(22) Nowak: Ann. de l'Inst. Pasteur, 1908, 22–52.

(23) Chapin, C. W.: Carbon dioxide in the primary cultivation of the gonococcus. Jour. Inf. Dis., 1918, xxiii, 342.

(24) Maitra, G. C.: Culture methods for the gonococcus. Indian Jour. Med. Res. July, 1919, vii, 219.
(25) Ruediger, E. H.: Exclusion of air in gonococcus culture. Jour. Inf. Dis., 1919, 24–376.
(26) Wertheim: (1) Reinzuchtung des Gonococcus Neisser Mittels des Plattenverfahrens. Deutsche Med. Wchnschr. 1891, Bd. xvii, S. 1351.
(2) Arch. f. Gynakol., 1902.
(27) Young, H. H.: The gonococcus: A report of successful cultivations from cases of arthritis, subcutaneous abscess, acute and chronic cystitis, pyonephrosis and peritonitis. Johns Hopkins Hospital Reports 1900, ix, 677–707.
(28) Grace, L. G.: A method of autoclaving bacteriologic media containing ascitic fluid. Jour. Lab. & Clin. Med., 1920, 5, no. iv, 253.
(29) Smith, I., and Fabyan: Centralbl. f. Bakteriol., 10, 1912, 61–549.
(30) Lentz: Centralbl. f. Bakteriol., 1910, 53–258.
(31) (1) Brons, C.: Beitr. z. Frage der Gram-negativen Diplokokken der Bindehaut. Klin. Monatsbl. f. Augenk. Stuttgart, 1907, Bd. xlv, S. I.
(2) Rothe: Über die Verwendung Verschiedener Zuckernährboden zur Differentialdiagnose der Gonokokken. Centralbl. f. Bakteriol. u. Parasitink. Jena, 1908. Abth. I, Orig. Bd. xlvi, S. 645.
(3) Elser, W. J., and Huntoon, F. M.: Studies on meningitis. Jour. Med. Res., Boston, 1909, xx, 402.
(32) Sternberg, G. M.: A Text Book of Bacteriology. Wm. Wood & Co., 1896, pp. 297.
(33) Kohman, E. J.: The so-called reduced oxygen tension for growing the meningococcus. Jour. Bacteriol. 1919, iv, no. 6, 571.

A STUDY OF THE ANTISEPTIC ACTION OF CERTAIN LOCAL ANESTHETICS

DAVID I. MACHT, Y. SATANI AND ERNEST O. SWARTZ

I. ANTISEPTIC ACTION OF LOCAL ANESTHETICS AGAINST STAPHYLOCOCCUS AUREUS AND B. COLI[1]

DAVID I. MACHT AND Y. SATANI

From the Pharmacological Laboratory, Johns Hopkins University and The James Buchanan Brady Institute, Baltimore, Maryland

II. A STUDY OF THE ANTISEPTIC ACTION OF BENZYL ALCOHOL AND OTHER LOCAL ANESTHETICS AGAINST THE GONOCOCCUS

ERNEST O. SWARTZ.

From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Maryland

Received for publication June 10, 1920

I. The Antiseptic Action of Local Anesthetics against Staphylococcus aureus and Bacterium coli

Although healing by first intention without infection is next to efficient anesthesia, the primary desideratum of every operation performed under local anesthesia, it is surprising to find that no investigation has been made concerning the antiseptic properties of local anesthetics. This may perhaps be due to the fact that the two most popular anesthetics, cocain and novocain, show nothing in their pharmacological action nor in their chemical structure, which would lead one to suspect that they

[1] This investigation was supported in part by a grant from the Council of Pharmacy and Chemistry of the American Medical Association.

were in any way germicidal or antiseptic in their properties; indeed, the solutions of these anesthetics are well-known to become contaminated with bacteria and molds. With the introduction of newer drugs for local anesthesia, the interest in the subject however has been revived. Macht and Nelson (1) have called attention to the fact that benzyl alcohol, the new local anesthetic discovered by one of the authors (M.) exhibited a distinct germicidal action on some bacteria. This observation stimulated the authors to carry out the present investigation. In the present research, the authors have undertaken a study of the antiseptic and germicidal properties of the most common local anesthetics in relation to some well-known bacteria. Such an inquiry was deemed desirable not only from a purely scientific point of view, but because also of a practical bearing, in at least two respects. In the first place, a local anesthetic which is also an antiseptic would tend to minimize the chances of infection after surgical operations. In the second place, such an anesthetic, when employed in certain regions or organs, would tend to destroy the bacterial flora, in those locations. Thus, for instance, in ophthalmological practice, such an anesthetic and antiseptic may be helpful in cases of infections of the eye. Again, and of still greater importance, a local anesthetic with antiseptic properties would be extremely desirable for use in urological practice for instillation into the urethra, the bladder, or ureters.

METHODS

The following drugs were studied: cocain, novocain, stovain, alypin, holocain, alpha-eucain, beta-eucain, apothesin or the hydrochlorid of diethyl-amino-propyl cinnamate, and benzyl alcohol. All these drugs were dissolved in physiological saline solution in various concentrations and their antiseptic action was studied on two microorganisms, the *staphylococcus aureus* and *B. coli*. Three methods of studying the problem were employed which are described below.

Series I

In this series of experiments, different amounts of a 1 per cent solution of the various drugs were introduced into 5 cc. bouillon medium, so as to make mixtures of various concentrations of the

TABLE 1

DRUG	ORGANISM	0.2 cc. (0.04 PER CENT)	0.5 cc. (0.1 PER CENT)	1 cc. (0.2 PER CENT)	2 cc. (0.4 PER CENT)
Cocain	Staphylococcus	Abundant	Abundant	Moderate	Moderate
	B. coli	Abundant	Moderate	Moderate	Slight
Novocain	Staphylococcus	Abundant	Abundant	Moderate	Slight
	B. coli	Moderate	Moderate	Moderate	Slight
Alypin	Staphylococcus	Abundant	Moderate	Moderate	Slight
	B. coli	Moderate	Moderate	Moderate	Slight
Stovain	Staphylococcus	Moderate	Slight	Slight	Negative
	B. coli	Moderate	Moderate	Moderate	Moderate
Holocain	Staphylococcus	Slight	Slight	Negative	Negative
	B. coli	Moderate	Moderate	Slight	Negative
Apothesin	Staphylococcus	Abundant	Abundant	Abundant	Negative
	B. coli	Abundant	Moderate	Slight	Slight
Alpha eucain	Staphylococcus	Moderate	Moderate	Moderate	Slight
	B. coli	Moderate	Moderate	Slight	Negative
Beta eucain	Staphylococcus	Moderate	Negative	Negative	Negative
	B. coli	Slight	Negative	Negative	Negative
Benzyl alcohol	Staphylococcus	Abundant	Moderate	Negative	Negative
	B. coli	Moderate	Slight	Negative	Negative
Control	Abundant	Abundant	Abundant	Abundant	Abundant
	Abundant	Abundant	Abundant	Abundant	Abundant

anesthetics, ranging from 0.04 to 0.4 per cent. A platinum loopful of staphylococcus or colon cultures was quickly introduced into the media thus prepared, and the test tubes were put into the incubator for twenty-four hours. The growth of the germs in the anesthetic bouillon mixtures was then observed. At the

same time control experiments were made with the same germs in the same bouillon medium but without the addition of drugs. The results of this series of experiments are tabulated in table 1.

Series II

In this series of experiments a loopful of staphylococcus or colon culture was introduced into solutions of the drugs in different concentrations (ranging from 0.01 to 5 per cent). These suspensions were then put into the incubator for different periods of time, ranging from ten minutes to twenty-four hours. They were then taken out of the incubator and rapidly centrifugalized. The fluid was then poured off and the organisms were washed with saline solution and separated again by centrifuging. The bacteria were then taken up with a loop and cultured on agar media. After incubating for twenty-four hours, the culture media were examined in order to determine whether any growth took place or not. For control experiment germs from the same cultures were suspended in normal physiological saline solution for different intervals of time, then centrifuged and planted on agar media and incubated for twenty-four hours. The results obtained in this series of experiments are shown in table 2.

Series III

In this set of experiments, a number of local anesthetics were incorporated or mixed with agar media in proportions of 0.5 or 1 per cent. Staphylococcus and colon organisms were then planted on the media. The cultures were incubated for twenty-four hours and the growth or non-growth of the organisms was then observed. For control experiment the same kind of organisms were cultured on plain agar media, without that mixture of drugs. The results of these experiments are shown in table 3.

TABLE 2

CONCENTRATION OF DRUG	KIND OF ORGANISM	EXPOSURE 10 MINUTES	EXPOSURE 30 MINUTES	EXPOSURE 1 HOUR	EXPOSURE 3 HOURS	EXPOSURE 24 HOURS
	Cocain					
per cent						
0.1	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	+++
0.5	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	+++
1.0	Staphylococcus aureus	+++	+++	+++	+++	++
	B. coli	+++	+++	+++	++	−
5.0	Staphylococcus aureus	+++	+	++	+	−
	B. coli	+++	+++	+++	+++	−
	Novocain					
1.0	Staphylococcus aureus	+++	+++	+++	+++	+
	B. coli	+++	+++	+++	+++	++
5.0	Staphylococcus aureus	+++	+++	+++	+++	++
	B. coli	+++	+++	+++	+++	++
	Holocain					
0.1	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	+++
0.5	Staphylococcus aureus	+++	+	+	+	−
	B. coli	+++	+++	++	++	−
1.0	Staphylococcus aureus	++	+	+	−	−
	B. coli	++	++	++	−	−
	Alpha eucain					
0.5	Staphylococcus aureus	+++	+++	+++	++	−
	B. coli	+++	+++	+++	+++	+
1.0	Staphylococcus aureus	+++	+++	+++	+++	−
	B coi	+++	+++	+++	+++	−
	Beta eucain					
0.5	Staphylococcus aureus	+++	+++	+++	++	−
	B. coli	+++	+++	+++	+++	−
1.0	Staphylococcus aureus	+	++	−	+++	−
	B. coli	+++	++	++	+	−

TABLE 2—*Concluded*

CONCENTRATION OF DRUG	KIND OF ORGANISM	EXPOSURE 10 MINUTES	EXPOSURE 30 MINUTES	EXPOSURE 1 HOUR	EXPOSURE 3 HOURS	EXPOSURE 24 HOURS
	Stovain					
per cent						
0.5	Staphylococcus aureus	+++	+++	+++	+++	−
	B. coli	+++	+++	+++	+++	−
1.0	Staphylococcus aureus	+++	+++	+	+	−
	B. coli	+++	+++	++	+	−
5.0	Staphylococcus aureus	+++	+++	+++	−	−
	B. coli	+++	++	−	−	−
	Apothesin					
0.5	Staphylococcus aureus	+++	+++	+++	−	−
	B. coli	+++	+++	+++	+++	−
1.0	Staphylococcus aureus	+	+	+	−	−
	B. coli	+++	+++	+++	+++	−
5.0	Staphylococcus aureus	−	−	−	−	−
	B coli	−	−	−	−	−
	Alypin					
1.0	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	−
5.0	Staphylococcus aureus	−	−	+	−	−
	B. coli	−	−	+	−	−
	Benzyl alcohol					
0.5	Staphylococcus aureus	+++	+++	+++	+++	−
	B. coli	+++	+++	+++	−	−
1.0	Staphylococcus aureus	+++	+++	+++	++	−
	B. coli	+++	+++	+++	+++	−
3.0	Staphylococcus aureus	−	−	−	−	−
	B. coli	−	−	−	−	−
	Methyl alcohol					
5.0	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	+++
	Ethyl alcohol					
5.0	Staphylococcus aureus	+++	+++	+++	+++	+++
	B. coli	+++	+++	+++	+++	+++

TABLE 3

MEDIUM	STRENGTH OF DRUG	ORGANISM	GROWTH
	per cent		
Cocain agar	1	Staphylococcus aureus B. coli	Abundant Abundant
Stovain agar	1	Staphylococcus aureus B. coli	Negative Negative
Apothesin agar	1	Staphylococcus aureus B. coli	Negative Negative
Alypin agar	1	Staphylococcus aureus B. çoli	Negative Negative
Benzyl alcohol agar	1	Staphylococcus aureus B. coli	Negative Slight
Benzyl alcohol agar	3	Staphylococcus aureus B. coli	Negative Negative

DISCUSSION

A study of the above tables will reveal the fact that while some of the substances studied exert practically no antiseptic or bactericidal action, others on the other hand exhibit quite distinct positive antiseptic and germicidal properties. The first series of experiments of course reveals more the antiseptic rather than the germicidal effect of the various drugs. In the second series, however, where the various organisms were exposed to the action of the various drugs for different periods of time and then washed, a failure to grow on agar afterwards points to a bactericidal or germicidal effect on the organisms. The third series of experiments is only interesting in connection with the first two series as corroborating the results obtained. Taken by itself, this group of experiments is of little value owing to the well-known objections to the use of impregnated culture media.

It is interesting to note that our two best-known and most widely used local anesthetics, namely cocain and novocain, are

entirely devoid of any antiseptic action. On the other hand, it will be noted that a number of other well-known anesthetics possess or exhibit definite antiseptic and even germicidal effects. Thus, it will be noted that alypin possesses such properties but only in concentrations of 5 per cent. Slight antiseptic properties are also exhibited by holocain, stovain and the eucains, but only after long incubation periods. A study of table 1, furthermore, reveals an interesting difference in the antiseptic properties between alpha-eucain and beta-eucain. It will be noted that the beta variety is more antiseptic in its action than the alpha variety. It is also interesting to note that the various antiseptic effects are not exhibited in the same degree in case of both of the organisms studied.

By far the most interesting drugs in connection with the present investigation are apothesin and benzyl alcohol. Both of these drugs exhibit quite a marked antiseptic action. It will be noted, however, that in series I, the antiseptic action of benzyl alcohol is more prominent. In series II, apothesin 5 per cent proved to be germicidal as was also benzyl alcohol 3 per cent. Inasmuch as, however, apothesin is used only in solutions of 1 per cent strength and certainly of not over 2 per cent on the one hand, and the benzyl alcohol is most efficient without being in the least toxic in concentrations of 3 to 4 per cent, it will be seen that the latter drug is the most antiseptic as well as the most germicidal of the local anesthetics studied. It is especially interesting to note (table 2) that neither methyl alcohol nor ethyl alcohol even in strengths of 5 per cent excited any antiseptic effect.

The above interesting findings in regard to the antiseptic action of some local anesthetics made it desirable to test some of the more efficient ones in respect to their effects on some other microörganism and more particularly in respect to their effects on the gonococcus. Studies on this subject have been made by one of the authors in association with Dr. E. O. Swartz, and the results were of sufficient interest to warrant a separate paper on the subject, which will be found to follow the present one.

CONCLUSIONS

1. The effects of a number of local anesthetics were studied on *Staphylococcus aureus* and *Bacterium coli* by three different methods.

2. It was found that some of the drugs, notably cocain and novocain, possess no antiseptic powers whatever, while others, notably apothesin and benzyl alcohol, exhibit distinct antiseptic effects.

3. These findings are deemed to be of interest not only in relation to healing of wounds, but also in respect to a direct effect on the flora of certain organs, notably the bladder and urethra.

II. A Study of the Antiseptic Action of Benzyl Alcohol and Other Local Anesthetics against the Gonococcus

From the standpoint of the clinician, it would be distinctly advantageous if the solutions used as local anesthetics in the urethra and bladder were at the same time distinctly antiseptic. The possession of definite antiseptic value in the anesthetic would do away with the necessity of a preliminary sterilization of the solutions. The anesthetic solution for local use in urology must be non-toxic, the dangers attending the use of cocain in the urethra being well-known. There is need of an antiseptic anesthetic which can be incorporated into a lubricant for use on instruments used in the urethra.

In the acute inflammations of the urethra—a great majority of which are due to the gonococcus—the injection of an antiseptic even in weak solutions is often so painful that the injection method of treatment has to be abandoned till after the acute symptoms have subsided. Without entering into a discussion as to the advantages and disadvantages of the injection method of treatment, it would seem that the use of an antiseptic, which is also an anesthetic, and non-toxic, would permit a relief of the pain on urination and an earlier treatment of these cases.

In this study, no attempt has been made to determine the minimum time or minimum concentration of the drugs killing

the gonococcus in a given period of time, but we have attempted only to ascertain the antiseptic and germicidal action of these compounds in strengths or concentration usually used in clinical work.

TECHNIQUE EMPLOYED

In making this study, the method described by Davis and Swartz (2) was employed. Fresh cultures of the gonococcus, twenty-four hours old, were used. The primary cultures were made from a case of acute gonorrhea in the male, the organisms being grown on veal infusion hydrocele agar at reduced oxygen tension after the method introduced by Swartz (3) and used exclusively in the laboratories of the Brady Urological Institute. The organisms were examined by Gram stain and sugar fermentation reaction to determine their identity. The organisms were washed from the agar slants by the use of warm normal salt solution—using about 5 cc. of saline solution for each slant—and the resulting gonococcus suspension kept on the water bath at 37.5°C. Different strains of organisms were used in tests made on different occasions, and controls were always made both at the beginning and end of each experiment to be sure of the viability of the organism and insure accuracy of results.

Drug dilutions were made in warm physiological salt solution and a mixture of drug solution and gonococcus suspension in varying proportions gave our final drug dilutions. Care was taken to use enough of the gonococcus suspension to give plenty of gonococcus in the tube for transference to the media for incubation.

After the organisms had been immersed in varying strengths of drug solutions for three minutes, on a water bath, they were centrifuged in a high power centrifuge for one minute, the supernatant fluid poured off, the precipitated organisms washed with normal salt solution by stirring, and again centrifuged. The precipitated organisms were transferred to gonococcus media slants, the oxygen tension reduced, and the tubes quickly incubated. The washing with salt solution was to remove the antiseptic and prevent its transference to and subsequent inhibition of

growth on the media. The work was so arranged that five minutes was the maximum time of contact of drug and organism.

Cultures were incubated for twenty-four hours at 37.5°C. and the results noted. If a single colony was present, it was counted as a failure of the drug to kill *all* the organisms. Cultures were incubated for twenty-four hours longer and results again noted. If colonies appeared after the second incubation period, it was considered that the late appearance was due to an antiseptic or inhibitory action of the drug on the organism.

The slants on which there was no growth at the end of forty-eight hours were incubated for five days more to rule out the possibility of prolonged inhibitory action of the drug. At the end of this time, slants on which no growth of gonococcus had appeared, were stroked with fresh viable gonococcus on a platinum loop and again incubated for forty-eight hours. The object of this procedure was to determine whether the organisms had been killed by the drug during the five minute contact period, or whether their growth had been inhibited by the small amounts of drug carried over to the medium on the loop, acting over the longer incubation period.

DISCUSSION

The method employed gives the germicidal value and does not give the inhibitory or antiseptic value, which is usually greater than the germicidal value. The test is rigid and favors the organism rather than the drug. If only one colony appears, it is counted as a failure of the drug at the given dilution to kill *all* the organisms.

The time chosen for contact between drug and organism—five minutes—probably does not represent the maximum time for antiseptic action in the urethra, and it is generally accepted that the germicidal value of many drugs is directly proportionate to the time of contact. While test tube experiments can give nothing but a rough evacuation of antiseptic values, yet from these tests it seems reasonable that our figures giving these values are low rather than high.

In these experiments, the temperature of the bacterial emulsions, physiological salt solutions and solutions of drugs was maintained constant at 37.5°C. The number of organisms used in each test was approximately the same. The age of the cultures was the same, and the culture media used both for primary culture and for transplants was of the same composition, reaction and consistency. The importance of maintaining these factors constant was emphasized by Chick and Martin (4) who showed that the resistance of a given bacterial culture to antiseptics is modified by its previous history and that an increased incubation temperature (within the limits of growth) increased the resistance of the organisms.

TABLE 4

	BENZYL ALCOHOL						APOTHESIN					
	Strength of solutions						Strength of solutions					
	C	3 per cent	2 per cent	1.5 per cent	1 per cent	C	C	2 per cent	1.5 per cent	1 per cent	0 5 per cent	C
24-hour reading	+	0	0	*3 +	+	+	+	0	0	0	0	+
48-hour reading	+	0	0	+	+	+	+	0	0	0	*5 +	+
7-day reading												
Tubes inoculated												
24-hour reading		+	+					+	+	+		
48-hour reading		+	+					+	+	+		

C = control tube; + = growth of gonococcus; 0 = no growth of gonococcus; * = number of colonies.

Solutions of the following drugs were studied: Alpha eucain, beta eucain, holocain, alypin, apothesin and benzyl alcohol.

Cocain and novocain solutions were found to be without any antiseptic action against the colon and staphylococcus and were not tested against the gonococcus.

A study of tables, included in this paper, shows definite antiseptic or germicidal action of all the drugs in certain concentrations, except beta eucain.

Alpha eucain, an isomere of beta eucain, inhibits the growth of gonococcus for the first twenty-four hours, but does not kill

them. Only a few colonies survived in the 1 per cent solutions, while the 0.5 per cent solution permitted a very luxuriant growth. Beta eucain solutions neither killed nor inhibited growth of gonococcus in this period of time in the dilutions used, which are concentrations usually used in clinical work.

Alypin killed the gonococcus in 5 per cent solutions, but permitted a growth in the 2.5 per cent solutions. There was no inhibitory action noted in case of this drug. Alypin solutions have a reaction of pH 4.5 on the hydrogen ion scale. The work of Davis and Swartz (5) showed that plain acid solutions, not of themselves germicidal, will kill the gonococcus in twenty minutes if of a hydrogen ion concentration more acid than pH 4.5, but

TABLE 5

	α-EUCAIN				β-EUCAIN			
	Strength of solutions				Strength of solutions			
	C	1 per cent	0.5 per cent	C	C	1 per cent	0.5 per cent	C
24-hour reading	+	0	0	+	+	+	+	+
48-hour reading	+	+	+	+	+	+	+	+
7-day reading								
Tubes inoculated								
24-hour reading								
48-hour reading								

C = control tube; + = growth of gonococcus; 0 = no growth of gonococcus.

that the gonococcus could survive immersion in warm solutions of acids of a hydrogen ion concentration of pH 4.5 for twenty minutes. Hence, the germicidal action of alypin is not due to the acidity of its solutions, but to some other factor.

Holocain hydrochlorate solutions have an acidity of pH 1.5—approximately that of tenth normal acid, and its germicidal action is probably due to its acidity, rather than to any specific action of the drug. Solutions of tenth normal acid kill the gonococcus in a few minutes.

Apothesin killed the gonococcus in five minutes in strengths of 1, 1.5 and 2 per cent or over. In 0.5 per cent solutions, a few colonies survived. These did not appear for forty-eight hours,

showing an inhibitory or antiseptic action even in 0.5 per cent solutions.

Benzyl alcohol invariably killed the gonococcus in five minutes in strengths of 3 and 2 per cent. In one experiment, a few colonies survived immersion in 1.5 per cent solution for five minutes. One per cent solution did not kill the gonococcus in five minutes.

Benzyl alcohol is of neutral reaction, having a hydrogen ion concentration of pH 7.0 and the germicidal action is not dependent on the acidity of the solution.

The antiseptic action of benzyl alcohol together with its lack of intoxicity, suggested its use as a gonococcocide, in acute gonorrhea. Work along this line is being carried on at present, and will be reported later.

TABLE 6

	HOLOCAIN				ALYPIN			
	Strength of solutions				Strength of solutions			
	C	2 per cent	1 per cent	C	C	5 per cent	2.5 per cent	C
24-hour reading	+	0	0	+	+	0	+	+
48-hour reading	+	0	0	+	+	0	+	+
7-day reading								
Tubes inoculated on 7th day								
24-hour reading		+	+			+		
48-hour reading		+	+			+		

C = control tube; + = growth of gonococcus; 0 = no growth of gonococcus.

After an incubation of seven days, all the tubes which showed no growth were inoculated with fresh gonococcus on platinum loop. All these tubes gave a growth of gonococcus, showing that there was no inhibition due to transference of drug to media on the platinum loop.

CONCLUSIONS

1. The germicidal value of certain concentrations of a number of local anesthetics against the gonococcus was determined. The solutions were of the same strength as those commonly used in clinical work.

2. Solutions of beta eucain have no antiseptic or germicidal action against the gonococcus. Alpha eucain solutions are antiseptic but not germicidal for the gonococcus.

3. Holocain, alypin, apothesin and benzyl alcohol are both antiseptic and germicidal for the gonococcus.

REFERENCES

(1) Macht and Nelson: Proc. Soc. Exp. Biol. and Med., 1918, xvi, 25.

(2) Davis, David M., and Swartz, Ernest O.: The testing of germicidal substances against the gonococcus. Forthcoming publication.

(3) Swartz, Ernest O.: Culture methods for the gonococcus: a report of experimental studies. J. Urology, vol. iv, no. 4, p. 325.

(4) Chick and Martin: Investigation of the laws of disinfection. Jour. of Hygiene, 1908, viii, 92–158, 654–697.

(5) Davis, David M., and Swartz, Ernest O. The prophylaxis of gonorrhea. Forthcoming publication.

A SIMPLIFIED TECHNIC FOR EPIDIDYMECTOMY

DANIEL N. EISENDRATH

Chicago, Illinois

The preservation of the orchis or body of the testis, during an operation for the removal of the tuberculous epididymis, is generally recognized to be highly desirable. The chief reason for this attempt to retain the testis is that the internal secretion of the viscus has its origin in the body proper. An additional factor which has an important bearing on this step is based on the knowledge that tuberculosis is primary in the epididymis and only extends to the testis proper at a comparatively late stage.

If one begins the removal of the tuberculous epididymis in the manner usually described, that is by separating the epididymis from the testis proper, it is very difficult to distinguish the vessels which enter the body or testis proper at its hilum. This is due to the many adhesions between the vessels, the vas deferens and the epididymis.

The conservation of the testis proper or body is dependent upon an adequate blood supply through the vessels which enter its hilum. If these are accidentally divided during the separation of the diseased epididymis, it becomes necessary to add an orchidectomy to the epididymectomy.

I have found that if one begins the isolation of the spermatic vessels at some point higher up where they are very accessible it is possible to perform the remainder of the operation (no matter how many adhesions to the scrotal tissues are present) with the blood supply of the body constantly in view, thus avoiding all danger of injury to the same. The operation of epididymectomy can be greatly simplified and in addition it is possible to divide the vas deferens high up without opening the inguinal canal.

The steps of the operation are as follows:

Step 1 (fig. 1). Incision. This is made of sufficient length to enable one to deliver the diseased epididymis as well as the non-diseased body of the testis (orchis). The middle of the incision usually lies at a point opposite the external abdominal ring.

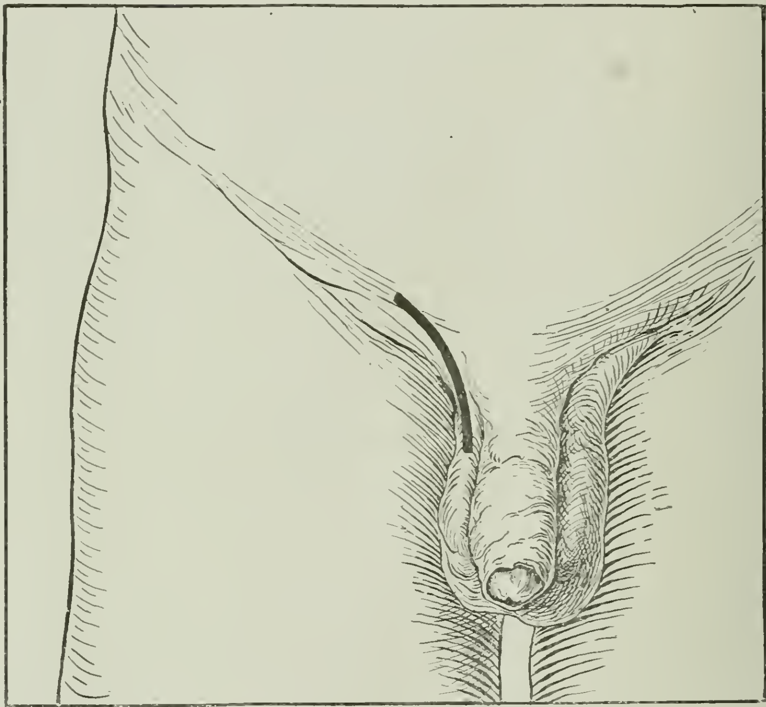


Fig. 1. Step 1. Incision Parallel to Cord, with Middle of Incision over External Ring

Step 2 (fig. 2). The spermatic cord is brought into the incision and the vessels accompanying the vas deferens, separated from the latter. Traction is then exerted upon the proximal portion of the vas until a considerable length of this structure has been pulled out. This procedure can be easily carried out without danger of tearing the vas, by a steady pull with the aid of a loop of catgut (fig. 2).

Step 3 (fig. 3). The vas deferens is grasped by two artery forceps close to the external ring and divided with a thin cautery blade as high up as possible. Contamination of the wound by the open end of the stump of a tuberculous vas is thus avoided.

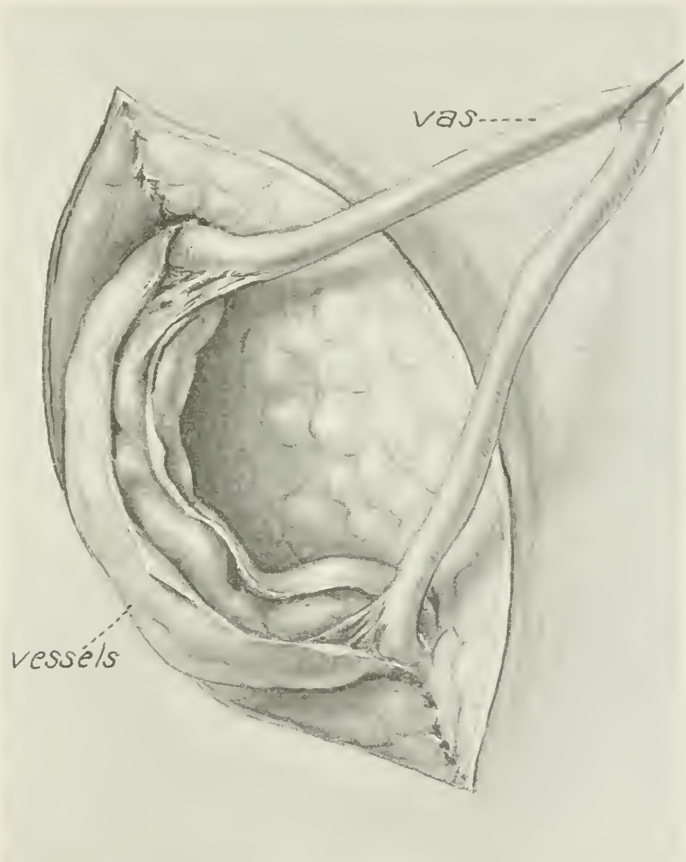


FIG. 2. STEP 2. VAS DEFERENS SEPARATED FROM ACCOMPANYING VESSELS OF SPERMATIC CORD

Note how easily vas can be pulled out of inguinal canal for some distance.

Step 4 (fig. 4). In order to avoid late bleeding from the proximal stump of the vas, it is ligated with chromic catgut or fine kangaroo tendon and the stump anchored to the tissues around

the external ring. The separation of the vas from the spermatic vessels is then continued down to the point (*A* of fig. 5) where the vessels enter the hilum of the testis. This is the essential

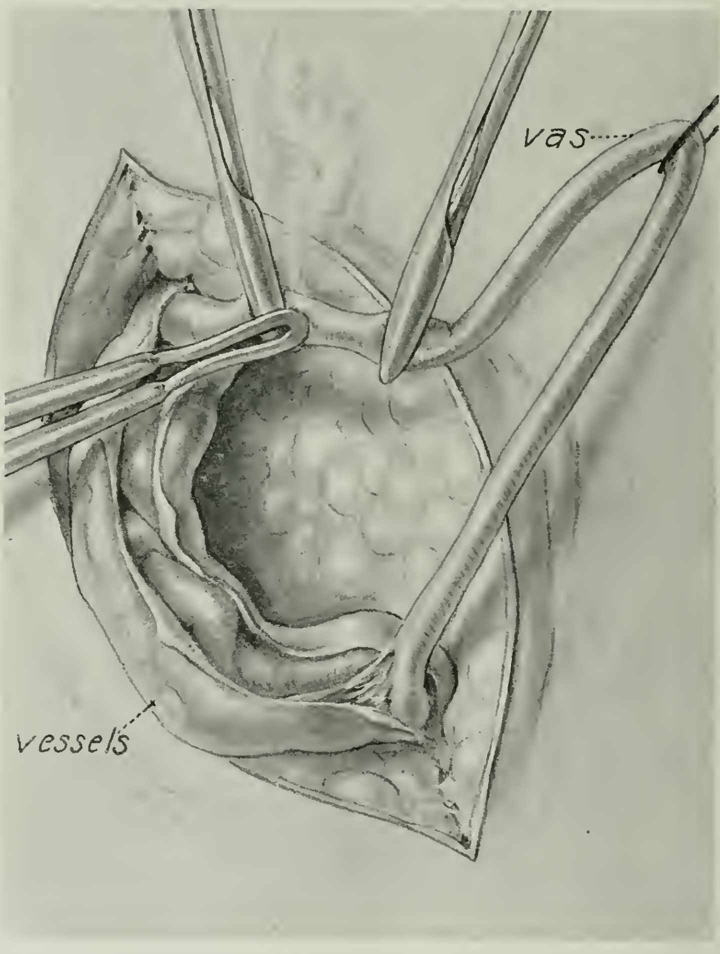


FIG. 3. STEP 3. VAS DEFERENS (HAVING BEEN PULLED OUT OF INGUINAL CANAL) IS DIVIDED HIGH UP WITH CAUTERY

feature of the simplified technic. The vessels can be readily isolated and seen to enter the body of the testis before their recognition becomes difficult as so frequently occurs when the operation is begun by removal of the epididymis from below.

Step 5 (*fig. 5*). The testis and epididymis (after separation of all adhesions to the surrounding tissues) are delivered through the incision shown in figure 1. The tunica vaginalis is opened (*A*

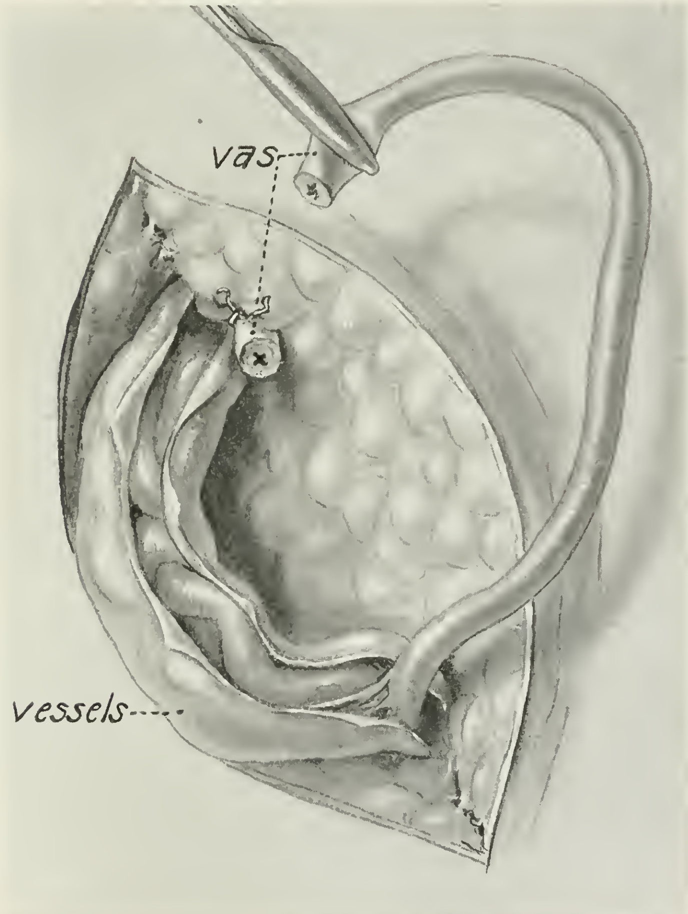


FIG. 4. STEP 4. THE PROXIMAL STUMP OF THE VAS DEFERENS IS LIGATED AND THEN ANCHORED INTO TISSUES AROUND EXTERNAL RING

of fig. 5) and the parietal portion of this sac excised. The separation of the epididymis from the testis proper is now begun by making an incision parallel to the hilum of the testis (*B* of fig. 5). A loop of catgut can be placed around the spermatic vessels

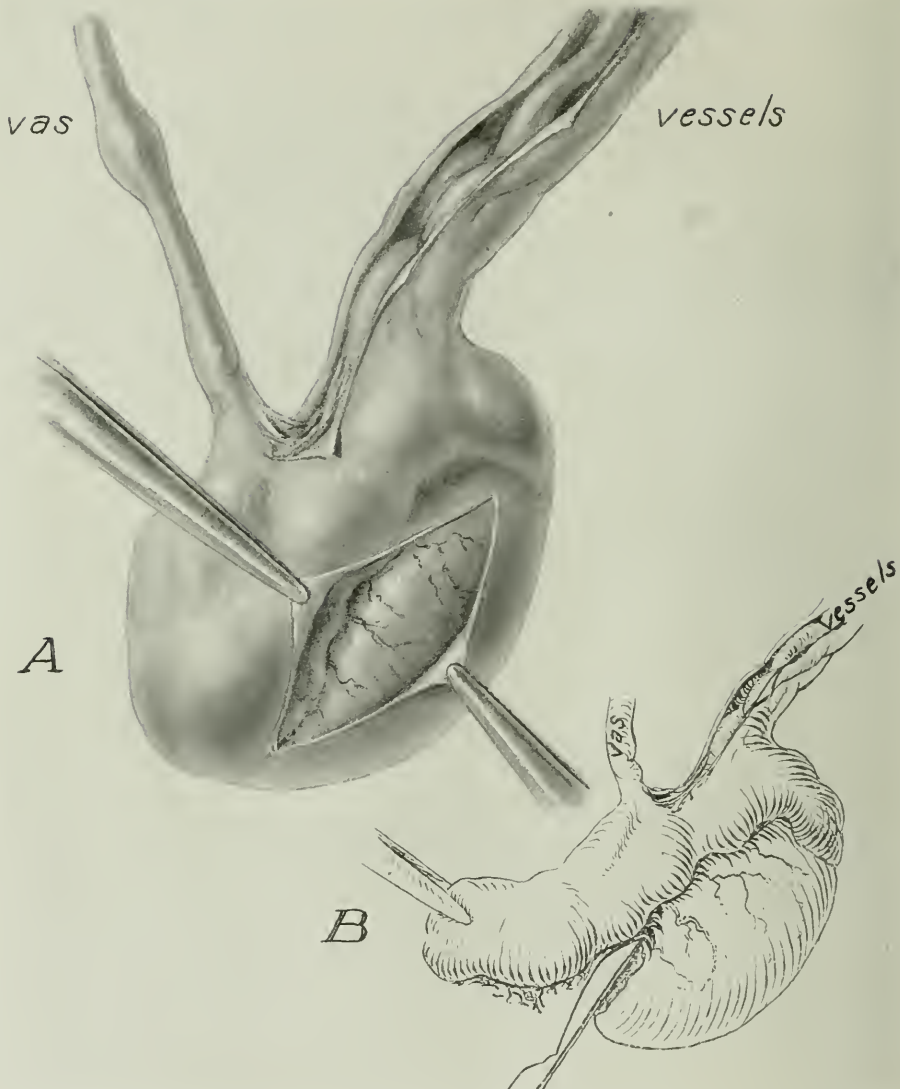


Fig. 5. A. Step 5. The Testis and Epididymis Having Been Delivered Through the Incision Shown in Figure 1, are Separated from Each Other as Far Down as the Hilum of the Testis

The tunica vaginalis is next opened and the diseased epididymis separated from the body of the testis as shown in *B*.

during this step of the operation in order to assist in their identification while the epididymis is removed by sharp dissection from the testis proper (fig. 6). This step will be found to have

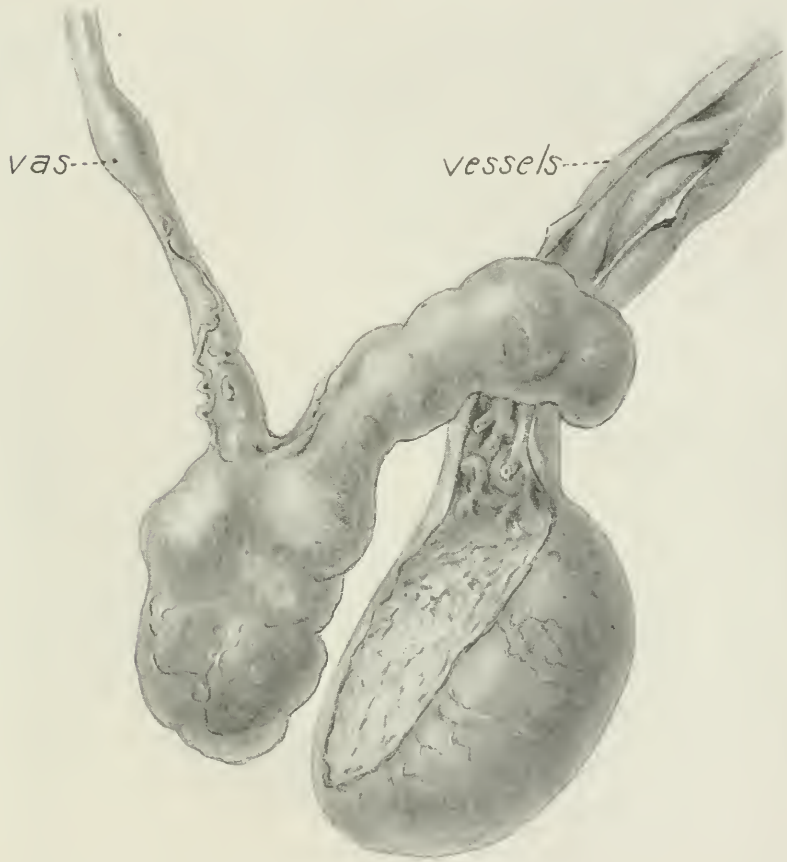


Fig. 6. The Tuberculous Epididymis and Vas Are Shown Completely Separated from the Testis Proper and its Vessels Without Injury to the Latter

been greatly simplified by the preliminary isolation of the vessels from the vas (figs. 2 to 5 inclusive).

Step 6 (fig. 7). After removal of the epididymis and vas the bed at the hilum of the testis proper is covered by approximation

of the edges of the visceral portion of the tunica vaginalis. The testis is replaced in the scrotum and all sinuses excised. The dartos scroti is closed with the finest size of plain catgut and the skin proper with very fine interrupted waxed silk sutures.

Fig. 7. Step 6. The Bed from Which the Epididymis Has Been Removed is Closed by Approximating the Edges of the Visceral Portion of the Tunica Vaginalis, the Parietal Portion Having Been Removed

I can warmly recommend this simplified technic after a trial in a sufficiently large number of cases to form an opinion as to its value in the conservation of the testis.

CHANGES IN ACIDITY OR ALKALINITY OF THE URINE PRODUCED BY B. COLI AS MEASURED BY THE FINAL HYDROGEN ION CONCENTRATION

ALFRED T. SHOHL

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

B. coli has the property of fermenting sugars and thus producing acid. The fermentation of various sugars has long been used as a method of differentiating subgroups in the colon-aerogenes family. The importance of acid production has recently been reëmphasized by Michaelis and Marcora (1912) and by Clark (1915), who showed that when grown in the presence of sufficient sugar, the cultures of B. coli reach a final or limiting acidity. This characteristic is considered a basic one in the recent studies of Winslow, Kligler and Rothberg (1920).

In the presence of a smaller amount of sugar (0.5 per cent glucose), certain of the B. coli reach the same limiting acidity, but others, after fermenting all the available sugar in the media, still grow and render the cultures alkaline. This phenomenon was utilized by Clark and Lubs (1915) as a means of differentiating B. coli into two classes. Those in the first group are acid to methyl red and those in the second group are alkaline to methyl red.

In the field of urology these facts are important because B. coli is the causative agent in 70 to 90 per cent of the infections of the genito urinary tract. The acidity or alkalinity of the urine determines both the growth of the organisms and the effectiveness of treatment. The general assumption has been that B. coli produces an acid condition of the urine, because it commonly produces acid in the media on which it is usually grown in the laboratory.

The text books of urology are vague or conflicting upon this point.

Pyelitis and pyelonephritis, when not associated with cystitis have an acid reaction of the urine.—Watson and Cunningham, vol. i, p. 463.

In chronic cystitis, the reaction is generally alkaline, or, if not, it soon becomes so unless due to the colon or tubercle bacillus.—Guiteras, vol. i, p. 456.

Of these bacteria, the colon, tubercle and typhoid bacilli and the gonococcus are usually associated with an acid cystitis, whereas staphylococcus, streptococcus and proteus group are generally alkaline.—J. R. Caulk, in Cabot's Urology vol. ii, p. 83.

The bacillus coli is found in acid or neutral urines.—E. L. Keyes, Jr., in Cabot's Urology, vol. ii, p. 436.

There was formerly a widely current belief that pus in the urine was always associated with an alkaline reaction. Such is not the case. A pyuria may be acid, neutral or alkaline; furthermore, the reaction gives no information as to the source of the pus. An alkaline pyuria is frequently found to proceed direct from the kidney by ureteral catheterization, and on the other hand, cystitis is most commonly associated with acid urine. The exact reverse of these conditions is also common. The main factor in determining the reaction of a pus-containing urine is the character of the infecting organism. The common acid forming organisms are: the bacillus coli communis, bacillus typhosus, the tubercle bacillus, and frequently the pyogenic cocci. The alkali-forming bacteria are the bacillus alkaligenes, the bacillus pyocyoneus, the bacillus proteus and sometimes the pyogenic cocci.—Kelly and Burnam, vol. i, p. 214.

The colon bacilli in the urine produce no appreciable effect on the reaction.—Park, Williams and Krumwiede, p. 786.

The reaction of the urine in infections with B. coli is significant in diagnosis and in treatment. Does an acid or an alkaline urine exclude the diagnosis of infection with B. coli when these are not found in smears or in cultures of mixed infections? Is the effect of B. coli on the reaction of the urine an important factor in the treatment of infections? These considerations have led us to a systematic investigation of the effect on the reaction of urine produced by cultures of B. coli.

THEORETICAL

A solution is acid because it contains hydrogen in the ionized state. The more ions present, the more acid is the solution. The concentration of hydrogen ions is subject to accurate measurement. A review of the determination of hydrogen ion concentration and its application to the problems of bacteriology has been furnished by Clark and Lubs (1917b).

The terminology which we employ is that devised by Sörensen, and has found general acceptance. The hydrogen ion concentration is represented by the symbol pH which denotes the negative logarithm of the concentration of hydrogen ions. The more acid the solution, the smaller the number which represents the pH value. Neutrality is represented by pH 7.0. Palmer and Henderson found the most acid urine to be pH 4.7, and the most alkaline urine to be pH 8.7.

In order to determine acid or alkaline reaction, one merely has to make a comparison between solutions of known hydrogen ion concentration and the sample, both containing the same indicator in the same amount. Thus, if one knows the initial reaction of the urine and the reaction after it has been inoculated with B. coli, one may determine whether acid or alkali has been produced.

EXPERIMENTAL

The organisms which we used for this study were supplied in part by Drs. Clark and Lubs and Dr. Bayne-Jones, for whose kindness we wish to express our thanks. The cultural characteristics of these organisms, both as to fermentative reactions and the final hydrogen ion concentrations on Clark and Lubs media, are shown in table 1. Equal samples of sterile urine titrated to varying pH, from pH 4.6 to pH 9.6, were prepared by the same methods as those used by Shohl and Janney, 1917. The urine was then inoculated with B. coli and the pH determined after an interval of fifteen days. Table 2 gives the initial and final values of pH of urine cultures of B. coli. It shows that, if the reaction of the urine is not acid or alkaline enough to inhibit

growth, the reaction progresses to a definite point which approximates pH 8.0. Cultures which at the start are more acid than pH 8.0 produce alkali. Cultures which are more alkaline than 8.0, produce acid.

In order to determine in more detail how the reaction progresses, urine was inoculated at pH 4.6, 5.6, 6.6, 7.6, 8.6, and read after 4, 24, 48, 120 and 168 hours. The results are shown in table 3 and are plotted in figure 1. No growth occurred at pH 4.6. All other cultures come to a final pH from 7.9 to 8.0. The same results were obtained by diluting the urine 10-fold and by varying the initial number of organisms.

TABLE 1

Characteristics of the organisms

NAME	DEXTROSE	SACCHAROSE	LACTOSE	RAFFINOSE	DULCITE	$\frac{CO_2}{H_2}$	FINAL pH CLARK AND LUBS' MEDIA
aab*	+	−	+	−	−	1.06	5.1
zv*	+	+	+	+	−	1.06	4.9
ze*	+	+	+	+	+	2.40	6.8
yv*	+	−	+	+	+	2.07	6.8
bu†‡	+	+	+				5.0
50†‡	+	+	+				4.9
X‡	+	+	+				5.0

* Obtained from Drs. Clark and Lubs.
† Obtained from Dr. Bayne-Jones.
‡ Pyelitis case.

This phenomenon is not dependent upon any special property of urine; it is also shown in cultures made upon meat infusion broth (see table 2). This was our stock medium and was initially pH 7.4. In this also, the cultures reach a definite final hydrogen ion concentration of 7.8–8.0. This is true both for strains of organisms which become acid and those which become alkaline to methyl red on 0.5 per cent dextrose media. Single strains of streptococcus and staphylococcus also attain a final pH 7.0–8.0. The results show clearly that B. coli, when grown in a sugar-free medium, consisting of either urine or bouillon, reaches a definite final hydrogen ion concentration, pH 8.0, which is alkaline.

TABLE 2

Final pH of coli

BOUILLON	URINE	
	Original pH	Final pH
8.3	8.0	7.5
8.5	9.4	8.5
8.5	YV 8.0	7.5
8 4	4.6	4.9
8.3	5.8	6.4
8 5	7.0	7.4
8 45	9.2	8.5
8.5	Bu 7.4	8.5
8.5	6.0	8.5
8.55	6.0	8.8
8.4	6.7	8.8
8.6	9.6	9.0
8.5	9.2	8.4
8.4	7.0	8.4
8.5	6.0	8.4
8.55	5.0	8.4
8.5	4.6	4.6
8.5	aab 9 6	7.4
7.8	7.4	7.4
7.0	X 9.0	7.2
8.3	8.2	7.2
8.0	8.6	7.2
8.4	Ze 9.4	8.4
8.2	4.8	7.2
7.6	4.6	7.2
7.8	ZV 4.6	4.6
Staph. alb. 8.35	4.8	7.2
Staph. aur. 7.0	7.2	7.8
Streptococcus 7.6	7.4	7.8
	9.2	7.9
	9.6	7.8
	Strep. 9.6	8.4
	9.2	8.4
	7.0	8.0
	6.0	7.4
	5.0	8.8
	Staph. aur. 5.6	8.0
	7.0	8.0
	9.2	8.5
	9.4	7.6
	8.0	8.5
	Staph. alb. 4.6	8.5
	5.5	7.6
	6.4	8.0
	7.4	8.2
	8.4	8.4
	9.4	8.6

TABLE 3

Hydrogen ion concentration of Bact. coli inoculated in urine of varying pH incubated at 37°C.

	pH				
At start	4.6	5.6	6.6	7.6	8.6
After 4 hours	4.6	5.6	6.6	7.4	8.2
After 1 day	4.6	6.1	7.0	7.6	7.8
After 3 days	4.6	6.8	7.4	7.8	7.9
After 5 days	4.7	7.9	7.9	7.9	8.2
After 7 days	4.7	7.9	7.9	7.9	8.0

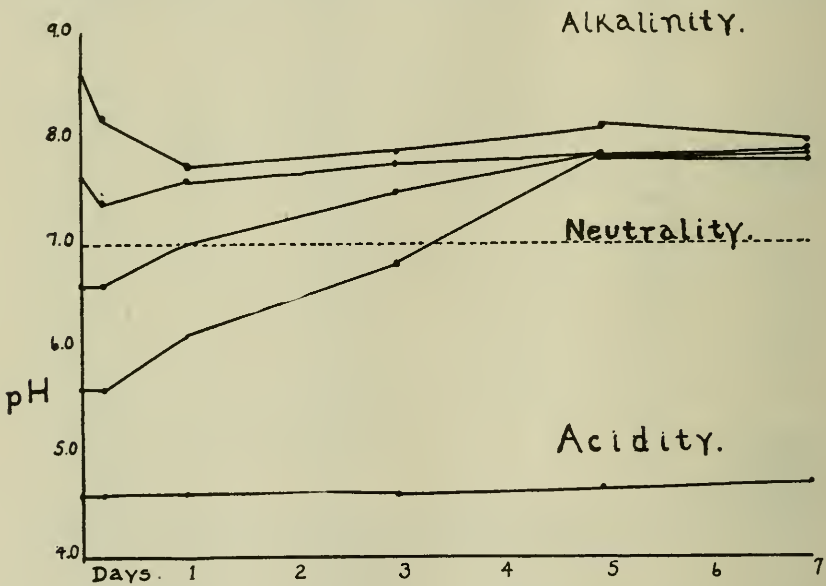


FIG. 1. HYDROGEN ION CONCENTRATION OF B. COLI INOCULATED INTO URINE OF VARYING pH, AND INCUBATED AT 37°C. FOR VARYING TIME

DISCUSSION

In the presence of insufficient sugar or in the absence of sugar, B. coli does not produce acid, as has been pointed out by Clark and Lubs (1915) and by Shohl and Janney (1917), whose experimental data agree closely with that presented above. Jordan (1911) studied the action of colon bacilli on the rate of putrefaction of urine. He states that no free ammonia was formed and

also that the cultures were not alkaline. Unfortunately, he used phenolphthalein as an indicator. This does not give a red color until pH 8.4–10 is reached. Therefore, his statement is not opposed to our findings. An extended inquiry into the mechanism of acid and alkali formation of B. coli can be found in the researches of Clark and Lubs (1917) and Ayers and Rupp (1918).

The question of the growth and acid formation of B. coli has a definite relation to the practical problems of urology. It is known that organisms are excreted with the urine in great abundance. Do these organisms grow rapidly and affect the reaction of the urine in the bladder? Shohl and Janney (1917) showed that in urine there was a definite and protracted "lag." Four hours must elapse before rapid growth occurs. We have also shown that coli produce no change in reaction in that time. Therefore, in cases where urine is not retained in the bladder more than four hours, the question of acid or alkali production has no bearing. The text books report coli associated with an acid urine. This does not mean that the organisms are the cause of the acidity. If the urine is acid, it is acid because of normal metabolism and normal acid excretion. If it is alkaline, it is alkaline because of diet or drugs. In cases with unobstructed urination, B. coli does not affect the reaction of the urine.

Since organisms multiply rapidly in the genito-urinary tract, the source of infection must be elsewhere than in the urine, or there must be retention of infected urine. In cases showing prostatic obstructions and a residual urine, the urine stays in the bladder long enough to have the growth of coli affect the reaction of the urine, and the alkaline urine in these cases may be due either to cocci or coli. In cases where there is residual urine, one expects to find an alkaline urine which may be due to the growth of B. coli. This must be taken into account in the treatment of such cases, if one expects to use acid drugs or drugs requiring an acid urine, or if one attempts to render the urine acid enough to cause inhibitory or antiseptic action.

CONCLUSIONS

1. B. coli in urine or sugar-free broth reaches a final alkaline reaction which is pH 8.0.

2. If the initial culture is more acid than this, alkali is produced. If more alkaline, acid is produced.

3. The reaction of the urine is not influenced by infections with B. coli when there is no obstruction. In cases showing obstruction, the alkali production from this source must be considered both in diagnosis and treatment.

REFERENCES

AYERS, S. H., AND RUPP, P. 1918 Simultaneous acid and alkaline bacterial fermentation from dextrose and the salts of organic acids respectively. Jour. Inf. Dis., xxiii, 188–216.

BRUENN, A. 1913 Uber das Desinfectionsvermögen der Säuren. Inaug. Diss., Berlin, 24 pp.

CABOT, H. 1918 Modern Urology. 2 v.

CHESNEY, A. N. 1916 The latent period in the growth of bacteria. Jour. Exp. Med., xxiv, 315–27; 387–418.

CLARK, W. M. 1915a The final hydrogen ion concentrations of cultures of B. coli. Jour. Biol. Chem., xxii, 87–98.
1915b The "reaction" of bacteriologic culture media. Jour. Inf. Dis., xvii, 109–136.

CLARK, W. M., AND LUBS, H. A. 1915 Differentiation of bacteria of the colon-aerogenes family by the use of indicators. Jour. Inf. Dis., xvii, 160–173.

CLARK, W. M., AND LUBS, H. A. 1917a Improved chemical methods for differentiating bacteria of the colon aerogenes family. Jour. Biol. Chem., xxx, 209–234.

CLARK, W. M., AND LUBS, H. A. 1917b The colorimetric determination of hydrogen ion concentration and its application to bacteriology. Jour. Bact., ii, 1–35, 109–135, 191–236.

GUITERAS, R. 1912 Urology, 2 v. New York. Appleton & Co., 8°.

KELLY, H. A., AND BURNAM, C. F. 1915 Diseases of the Kidneys, Ureters and Bladder. 2 v., New York. Appleton & Co., 8°.

HENDERSON, L. J., AND PALMER, W. W. 1913 On the extremes of variation of the concentration of ionized hydrogen in human urine. Jour. Biol. Chem., xiv, 81–85.

MICHAELIS, L., AND MARCORA, F. 1912 Die Säureproduktivität des Bacterium Coli. Ztschr. f. Immunitatsf., xiv, 170–173.

PARK, W. H., WILLIAMS, A. W., AND KRUMWIEDE, C. 1920 Pathogenic Microorganisms. Philadelphia, Lea & Febiger, 786 pp., 8°.

SHOHL, A. T., AND JANNEY, J. H. 1917 The growth of Bacillus coli in urine at varying hydrogen ion concentrations. Jour. of Urology, i, 211–229.

WATSON, F. S., AND CUNNINGHAM, J. H. 1908 Urology. 2 v. Philadelphia, Lea & Febiger.

WINSLOW, C.-E. A., KLIGLER, I. J., AND ROTHBERG, W. 1920. Studies of the classification of the colon-typhoid group of bacteria with special reference to their fermentative reactions. Jour. Bact., iv, 429–503.

THE PASSAGE OF BACTERIA FROM THE URINARY BLADDER INTO THE BLOOD STREAM[1]

J. A. H. MAGOUN, JR.

Rochester, Minnesota

It is an established clinical fact that in the acute infections of the renal pelvis, chills, fever and sweats are comparatively common, whereas in acute infections of the bladder, without complicating pathology, the manifestations of absorption are rare. Since in a former article (3) I had shown that the passage of bacteria from the pelvis of the kidney into the blood stream may readily take place, it was deemed advisable to study the process with reference to the urinary bladder.

In 1890 Guyon and Albarran stated that there is no absorption from the normal bladder, but in a bladder which has been subjected to acute retention of the urine, the epithelium is lost and absorption may occur. They recovered organisms from the heart's blood of a guinea pig and of a dog after injection of bacteria into the bladder, the penis having been ligated previously. Sampson doubly ligated the right ureter and excised a portion of it. The mucosa of the bladder was injured, a small stone placed in the bladder, and the incision closed. Ten cubic centimeters of a twenty-four hour culture of *Staphylococcus pyogenes aureus* were then injected into the bladder. One dog, killed the next day, showed a pyonephrosis of the right kidney, and the organism was recovered in the blood, liver, gallbladder, urinary bladder and both kidneys. The examinations of the other three dogs were negative.

Guyon and Albarran and Sampson do not state whether or not both ureters were ligated. It is possible, although not prob-

[1] From the Division of Experimental Surgery and Pathology and the Section on Urology of The Mayo Foundation (University of Minnesota) and the Mayo Clinic.

able, that if both the ureters had not been ligated the bacteria might have gained entrance to the kidneys either by the ureteral lumen or periureteral lymphatics and, once lodged in the kidney, they could easily enter the circulation.

Macht has shown that various alkaloids such as apomorphin and morphin, certain antiseptics, anesthetics and salts, are poorly absorbed by the bladder mucosa.

METHOD FOLLOWED IN EXPERIMENTS

Female dogs were used in all the experiments. Light ether anesthesia was maintained. A steel catheter was placed into the bladder and the urine expressed. A small low midline incision was made and a double ligature passed around the catheter at the juncture of the bladder and the urethra; each ureter was then firmly ligated. At variable pressures a dextrose-broth culture of *Bacillus prodigiosus* of approximately forty-eight hours was allowed to flow into the bladder.

Two hours after the entrance of the bacteria into the bladder, cultures were taken from the heart's blood, lungs, liver, vena cava, both kidneys, and the wall of the bladder.

The experiments may be divided into three series. In the first series of eleven experiments the bladder was normal and the solution was injected under low pressures. In the second series of two experiments the bladder wall was normal but a pressure of from 30 to 40 cm. of water was employed. In the third series of four experiments an acute cystitis had been produced a few hours earlier by the injection of tincture of cantharides. The results of the experiments are summarized in table 1. In experiments 6 and 8 a relatively high intravesical pressure was used. Acute cystitis was produced in experiments 7, 9, 11, and 13. In all the other experiments the bladder mucosa was normal and the pressure was low.

The results in the three series were uniform. *Bacillus prodigiosus* was obtained only in the wall of the bladder and in this organ in but three experiments.

Our experiments show that absorption of bacteria through the normal bladder mucosa or the acute inflamed mucosa must be relatively slight, if it occurs at all. This fact is the more strongly emphasized by a comparison with the ease by which the bacteria pass through the pelvis of a normal kidney into the blood stream. The results appear to show that the bladder, as compared with the kidney, is an infrequent source of blood stream infection. It should be noted, however, that all the experiments were acute,

TABLE 1

Bacterial absorption from the bladder

EXPERIMENT	PRESSURE IN BLADDER CENTIMETERS OF WATER	CONDITION OF BLADDER	CULTURES FOR BACILLUS PRODIGIOSUS
1	2	Normal	Negative
2	2	Normal	Positive in bladder wall only
3	3	Normal	Positive in bladder wall only
4	3	Normal	Negative
5	1	Normal	Negative
6	30–40	Normal	Negative; bladder wall purple-red
7	7	Acute	Negative
8	30–40	Normal	Negative
9	7	Acute	Negative
10	6	Normal	Negative
11	3	Acute	Negative
12	7	Normal	Negative
13	7	Acute	Negative
14	8	Normal	Negative
15	7	Normal	Negative
16	7	Normal	Negative
17	10	Normal	Positive in bladder wall only

and dealt with the absorption of nonpathogenic bacteria through normal tissue. It is possible that pathogenic bacteria, located in the wall of a chronically infected bladder, may pass into the lymph or blood stream, and thence be carried to other organs.

These experiments have shown that bacteria do not readily pass through the mucosa of the bladder; nevertheless this mucosa has the power of absorption of certain dyes such as phenolsulphonephthalein and indigo carmin. This selective absorption of the bladder mucosa is under further investigation.

REFERENCES

(1) Guyon, F., and Albarran, J.: Anatomie et physiologie pathologiques de la retention d'urine. Arch. de méd. expér. et d'anat. path., 1890, ii, 181–221.

(2) Macht, D. I.: On the absorption of drugs and poisons from the bladder and the urethra. I. Absorption of apomorphin and morphin. Jour. Urol., 1918, ii, 43–49. II. Absorption of various alkaloids, antiseptics, local anesthetics, and salts. Jour. Urol., 1918, ii, 211–226.

(3) Magoun, J. A. H., Jr.: Pelvis of kidney as possible source for infection of blood stream. Preliminary report. Jour. Am. Med. Assn., 1920, lxxiv, 73–75.

(4) Sampson, J. A.: Ascending renal infection; with special reference to the reflux of urine from the bladder into the ureters as an etiological factor in its causation and maintenance. Bull. Johns Hopkins Hosp., 1903, xiv, 334–352.

VENEREAL PROPHYLAXIS IN CIVILIAN LIFE[1]

HENRY L. SANFORD
Cleveland, Ohio

Anyone who had an opportunity to observe the results obtained by the use of venereal prophylaxis in our army during the late war, and especially in France, must have been impressed with its efficiency as a preventive of venereal disease. The fact of its efficiency under conditions of timely and proper administration has been so abundantly proved by numerous sets of carefully taken statistics in military life, that we need not quote them here.

Accepting this efficiency as an established fact, as a natural sequence the thought arises why should not the civilian public be given the same protection against venereal infection that we thought so vitally necessary to our soldiers. It is the object of this paper to offer some considerations on this subject.

Let us anticipate certain objections which may be raised to such a plan. The most obvious one is that the conditions of military life with its means of enforcing discipline, favorable to the almost universal application of prophylaxis, do not obtain in civil life. This is entirely true. The reason for insistence on prophylaxis while the war lasted was to keep the men fit to fight, and after the armistice it was to keep them fit to go home. Among the five million men in uniform the rate of incidence of venereal disease was gratifyingly low in comparison to the rate of exposure. Efficient prophylaxis was the sole explanation. Shall we then immediately lose interest in the health of five million men from a venereal standpoint, the day they change their uniform for civilian dress, to say nothing of other millions of men who never were fortunate enough to have been protected

[1] Read before the Genito-Urinary Section of the Ohio State Medical Association June 1, 1920.

by prophylaxis? If means for taking venereal prophylaxis in civilian life should be established, it would be offered as an opportunity to escape infection and not as a military requirement. The need for protection against infection exists now just as in war time, and though we have not the military means of making men who expose themselves to infection take precautions, should we on that account refuse them the opportunity of so doing? If we do, it means that we are willfully turning our backs on an assured percentage of infection when we know how to prevent it.

It may be objected that if community prophylactic stations were established, the demand for them would be small. It is true that it would take some time for the public to learn that they were available, and many might at first hesitate to use them. Any man however, who had been protected against infection by prophylaxis during his army service would certainly recognize their value, and that there is a definite demand for such stations is shown by the fact that we have been asked in the past few months by at least twenty ex-service men why the protection they were given in the army should not be available now. We feel that demand for prophylactic facilities would develop fast if the opportunities were once offered.

A third obvious objection will be raised on moral grounds, that if it became generally known that prophylactic stations were available where the possible consequences of sex indulgence could be avoided, all fear of infection would be removed and the assurance of safety would simply serve to encourage irregular conduct. This criticism would be just if prophylaxis were planned and established in that spirit. But the whole problem rests on the undeniable fact that until human nature changes, extra-marital intercourse will continue, with all the dangers of infection it implies. The preachings of moralists, the teachings of physicians, the enactment of laws, and the fear of punishment or infection, all of them combined have not succeeded in stopping man from satisfying an instinct which is among the most primal, and there seems to be no indication of any immediate radical change in human nature.

It is not that we do not heartily approve of the value of the proper presentation of the principles of sex hygiene, of the teaching of continence in the unmarried, or that we fail to appreciate the civic and social betterment agencies which provide playgrounds, athletics, and amusements to distract attention from sex matters by a healthful fatigue. It is because we realize that though these agencies accomplish a vast amount of good, there is always a considerable percentage of individuals who either will not profit by them, or who in spite of them, continue to expose themselves to venereal infection, and with discouraging success. To deny this percentage is to deny facts. To ignore it by saying "What more can we do?" is like telling a child to keep away from a hot stove, and then leaving it to burn itself. It seems to us the answer to the question is to employ a constructive means of prevention which wide experience in the army proved to be effective, and to offer it to the public for the benefit of the known percentage of individuals whom other agencies seem powerless to control.

For years the medical profession has been doing its best to patch up this steady percentage of individuals who apply for treatment only after their infection is well established. For years physicians have realized that locking the stable door after the horse is stolen is an inefficient and halfhearted way of handling the problem, especially as patients of this sort are hard to control, and treatment is seldom carried through to a complete cure, so that the individual's infection becomes not only a danger to himself, but a menace to others.

Many of us have doubtless reproached ourselves in the past for this non-constructive attitude, but we felt that public opinion was not yet ready to accept the radical proposal of civilian prophylactic stations. In the past few years however, the public has constantly been getting better informed about venereal disease, and now is becoming more interested in means for its prevention. It has taken the war, however, to teach us many things, and to those of us who worked on the prevention of venereal disease among troops, the lesson of the well nigh absolute efficiency of prophylaxis was so thoroughly demonstrated that we feel it noth-

ing less than a duty on our return to civilian life, to do everything in our power to offer the civilian public the protection we saw so effectual for the soldier.

We feel prophylaxis should be offered the public for two reasons—as an economic measure, and to safeguard the public health.

Let us try to form an estimate of the economic loss caused by venereal disease in the community. The Social Hygiene Bulletin, in an article on the relative efficiency of venereal disease reporting in the various states, estimates that during the year 1919, there were 217,491 cases of venereal disease in Ohio. This figure was obtained by multiplying the estimated population of the state on January 1, 1919, by the percentage of venereal disease in Ohio troops in the second million of the draft. As men of draft age were drawn from all classes of society, it is probable that the estimate contains as small a margin of error as any that could be obtained. It is an understatement to say that each one of these 217,491 cases costs the community $100, for its primary care, whether the individual patient pays the money out of his own pocket to a private physician, or whether he is treated at a dispensary. Cases of gonorrhea and chancroid usually imply shorter duration and outlay for drugs than properly treated cases of syphilis. Assuming this average we have an item of nearly twenty-two millions of dollars for primary care.

To this must be added the time lost from work due to disabling complications of venereal disease, especially epididymitis, prostatic abscess, and gonorrheal rheumatism. Supposing 60 per cent of the total cases in Ohio are gonorrheal, and that 20 per cent of the 60 per cent have a disabling complication which would keep them from work with an average time loss of three weeks apiece, and that each patient had a minimal earning capacity of $40 a week, we have the further item of 130,494 cases losing wages of $120 each, making a further economic loss of $15,652,000.

This analysis does not include the secondary effects of venereal disease with the disability, loss of earning power and shortening of life they produce, such as urethral stricture, the mutilating operations, sterility, and invalidism following gonorrhea in women, and the brain and cord lesions of syphilis. The actual

economic loss to the community resulting from these secondary effects is difficult to estimate, but to the thirty-seven millions of the first two items it is safe to add in loss of earning power and shortening of life enough to bring the total up to fifty millions of dollars—the sum venereal disease costs the people of Ohio in a year. The question whether it is worth while to try to save fifty millions a year, which are now being spent on entirely preventable diseases is not open to argument. The only point we have to make is whether, in addition to the various agencies that are now in operation to prevent the occurrence of venereal disease, but which, commendable as they are, are falling short of success by a margin of fifty millions of dollars a year of economic loss, we should provide still another agency, that of venereal prophylaxis for the public, the only truly constructive medical agency in the lot.

Aside from the economic loss, reckoned in dollars and cents, due to venereal disease, each case is a potential menace to public health as a result of innocent or criminal transfer of infection from the patient to others. Health authorities throughout the country recognize this, and in most states venereal diseases are among the contagions reportable under the state law. That these laws are not observed is shown in the article quoted above, in which the efficiency of venereal disease reporting varies in figures submitted by forty-two states from 19.6 per cent in Massachusetts to 0.7 per cent in Wyoming. These figures do not pretend to be accurate, but even allowing a large margin of error, they show the inefficiency of the system. The attitude of health authorities in insisting on the reportability of venereal disease is logical and inevitable, but physicians would not be put in the position of having to report their cases of venereal disease if their patients had taken proper and timely prophylaxis, in fact they would not be patients.

If these considerations have at all persuaded you that venereal prophylaxis in civilian life is justifiable and advisable, we have to consider by whom the prophylactic stations should be controlled and maintained. It seems to us logical that as the whole affair is one of public health, that these stations should be under

the Department of Public Health, preferably under state rather than municipal control, as only in this way could prophylaxis be offered to country districts.

The plan could be put in operation by establishing one or more stations in a large city, extending the system as it proved successful. If these stations could be placed in already existing municipal or state health centers, the overhead expense of their maintenance would be greatly reduced.

We believe that no attempt should be made to camouflage their purpose by calling them "Early Treatment Stations," but that they should be known as Prophylactic Stations, and their object clearly understood. Experience in the army proved that to function at full value, these stations must be open night and day, requiring the services of a night attendant. The day attendant might be recruited from the day personnel of the health center.

It is not necessary before this body to go into the details of equipment or technic of administration of treatments, except to say that much was learned during the war of the efficacy of various prophylactic agents, and especially of the almost specific value of thoroughly applied green soap as a preventive of chancroid, and conversely, the almost total failure of calomel ointment to prevent its development.

In this connection we believe that a sharp distinction should be drawn between the value of a properly and scientifically given prophylactic treatment at a prophylactic station and the use by the individual himself of a self-administered prophylactic package. We feel there is a distinct place for the first but that there should be none for the second, after prophylactic stations once become available.

In France during the war, individual prophylactic packets were issued to those whose duties took them on trips where for days or weeks they would be out of touch with our own army units. These packets were regarded solely as an emergency issue, their dependability was never considered equal to that of a proper treatment at a regular prophylactic station and they were never employed as a routine measure.

In civilian life, we believe that the possession of prophylactic packets by an individual, with the fancied assurance of safety against infection they inspire, is a distinct temptation to exposure—a wholly different situation from the man who seeks prophylactic treatment only after an unpremeditated contact. The usual prophylactic packet, which consists of a gelatine capsule of calomel ointment, further gives a false sense of security against infection because the average individual will not use it correctly or with sufficient preliminary cleanliness. This results in unexpected infections. None of these arguments apply to prophylactic treatments properly given at a prophylactic station.

If the proposal to offer venereal prophylaxis to the public receives the backing of the medical profession, the first task of those who are interested in the plan will be to educate the public as to the need for it, and to meet the moral and social objections which are sure to be raised. It seems to us that the way to accomplish this is to support with all our power the present moral and social agencies now operating to prevent venereal disease, and to offer prophylaxis as an added measure to stop the economic loss now occurring in the percentage of the community which the present agencies are not successful in reaching.

RENAL TUBERCULOSIS COMPLICATED BY INGUINAL RENAL FISTULA, TRANSVERSE MYELITIS AND RENAL CALCULUS[1]

J. DELLINGER BARNEY AND W. J. MIXTER

Boston, Massachusetts

The following case of renal tuberculosis presents such rare complications and unusual features that we feel it should be recited to the members of this Association and put on record.

L. W. Male, forty-six years old.

Family history. Unimportant.

Past history. Gonorrhea several times in youth. Symptoms of stricture for years. In October, 1915, acute retention. External urethrotomy at Massachusetts General Hospital. Good recovery.

Readmitted to the West Surgical Service in March, 1918 with a painful, tender mass in left groin of 3 weeks duration. Had had a persistent cough with loss of weight and "malaria" during the winter. Mass in groin soon became fluctuant and was incised with the escape of about a quart of thin purulent fluid (apparently not suggesting urine). Urine was cloudy, with much pus and a few blood cells. Reflexes normal. Patient discharged in two weeks with wound practically closed.

Readmitted to the West Surgical Service in May, 1919, with abscess of left groin similar to the one in 1918 and of five days duration. Much pain. Physical examination showed abscess of left groin just above Poupart's ligament. Wound of previous operation completely healed. Perineum is red and brawny with a small sinus, evidently connecting with urethra. Reflexes normal; urine cloudy, with albumen, and a large amount of pus. X-ray of spine and pelvis negative. Orthopedic surgeon can find no cause in the spine for inguinal abscess. Sputum negative.

[1] Read at the thirty-second annual meeting of the American Association of Genito-Urinary Surgeons, Mayo Clinic, Rochester, Minn., May 30, 1920.

Abscess opened May 5, 1919, with the escape of much thick pus. Culture showed B. coli. Abscess cavity admitted one's finger and led obliquely around and upward under the psoas muscle. Patient discharged in three weeks with wound almost closed.

Present illness. Readmitted to the West Surgical Service December 12, 1919. Inguinal sinus has drained more or less constantly since May. About a week ago noticed numbness of feet and legs with weakness. This has progressed so that patient is now unable to walk. Owing to this condition, which at time of entrance was the predominant feature of the case, one of us (W. J. M.) was asked to study the patient from a neuro-surgical standpoint.

Physical examination. Heart and lungs negative. Abdominal examination negative except for sinus in left groin just above Poupart's ligament. This sinus drains thin pus, the drainage being increased by pressure over left kidney. Scrotum red and tender. Perineum red and brawny with one or two small fistulae. Calibration of urethra shows multiple strictures. Neurological examination—Cranial nerves and upper extremities negative. Incontinent of urine and feces at times. Voluntary movement of all muscle groups of both legs, but marked general weakness and considerable involuntary twitching. Tendon reflexes lively and equal. Right clonus and Babinski. Left pseudo-clonus not sustained. Left plantar normal. Cremasteric and abdominal reflexes absent. Epigastrics equal and active. Sensation definitely diminished to brush to 10th or 11th dorsal vertebra. Pinpoint exaggerated and suggests "electric shock." Upper level not sharply defined. Saddle area of increased anesthesia about tip of coccyx. Spine shows prominence of 8th and 10th dorsal vertebrae. No limitation of motion, no pain. Blood pressure 148/80.

Lumbar puncture (by Dr. James B. Ayer). Clear colorless fluid. Pressure 160 mm. After 5 cc. withdrawn pressure 120 mm. Pulse and respiratory oscillations normal. Protein (alcohol) ±, Nonne negative. Sugar none, cells none.

Blood Wassermann negative. Spinal fluid moderately positive.

X-ray of spine on two occasions shows no evidence of Pott's disease, thus confirming a previous orthopedic opinion.

X-ray of kidneys shows a large shadow which has the same shape as pelvis of kidney on the left side.

January 2, 1920. Neurological condition somewhat improved since admission three weeks ago.

External urethrotomy (J. D. B.) with excision of sinuses and scar tissue and drainage of a large perineal abscess. Wound closed in with plastic flaps. Perineal drainage.

January 18, 1920. Good convalescence. Myelitis still improved. Perineal wound nearly closed.

Cystoscopy (J. D. B.) shows essentially normal bladder mucosa. Right ureter normal and admits no. 6 catheter to kidney. Urine clear, sediment negative, phenolsulphonephthalein appears in $4\frac{1}{2}$ minutes (intravenous) with 30 per cent in 1000 cc. in fifteen minutes. Left ureter retracted, contracted, red and edematous. Catheter will not engage in its oreific; no jet seen. Nothing to suggest either a third ureter or a fistulous opening in the bladder.

Bladder urine cloudy, acid, 1012, albumen, slight trace, no sugar. Sediment shows much pus and an occasional red blood cell. White count varies from 12,000 to 26,000. Hgb. 80 per cent.

January 27, 1920. Transferred to the Genito-Urinary Service. Left nephrectomy (J. D. B.). Kidney large, thin walled, filled with pus and remarkably adherent so that it was torn in several places during delivery which was of necessity intracapsular. Ureter much thickened, indurated and adherent. Parallel to and internal to it there was another structure of about the same size and consistence which looked and felt much like a second ureter but lined with grayish granulation tissue. A finger could be inserted down this tract in the direction of the groin, and upward to the kidney pelvis where a large stone could be felt. During the delivery of the kidney many small pieces of stone escaped.

Pathological report (Dr. James Homer Wright). Pyramids and calices are represented by cavities bordered by inflammatory material. Pelvis is dilated and tissue about it porky and inflammatory. Bloody to purulent fluid bathes cavities. Microscopic examination shows appearance of tuberculosis. Unfortunately the specimen was presented to the pathologist minus the calculus and with no statement as to its unusual features. From our own observation of the calculus, at the time of operation we are positive that it was not simply an incrustation of the renal pelvis with lime or phosphatic salts, nor was it an area of calcification so commonly seen in cases of renal tuberculosis.

February 3, 1920. Discharged relieved. Patient was in a precarious condition for some days after operation. Perineal wound practically closed. Kidney wound closed except for a small granulating area. Inguinal sinus closed. Patient can now use his legs fairly well and sensation is returning.

Patient has reported to us twice in the past few weeks. Has gained 15 to 20 pounds weight, feels strong and well. Perineal wound entirely closed, sounds to 28 F. passed easily. Kidney wound still discharging a small amount from one sinus. Inguinal wound entirely healed. Can walk an almost unlimited distance without cane or crutches and with no fatigue. Sensation now practically normal. Sphincters, normal.

It will be noted that although this patient was under more or less constant observation since October, 1915, both in the Out-Patient Department and in the House and was seen by several different House Officers and surgeons there was nothing at any time to arouse the suspicion of renal tuberculosis or, in fact, of any kidney lesion. He also furnishes another example of the silence of renal calculus. It is certainly remarkable that an inflammatory condition of the kidney and its pelvis as well as of the perinephric tissues giving rise to an inguinal fistula should not also have called the attention of the patient, if not of the surgeon, to its presence at one time or another.

Bladder symptoms were conspicuous by their absence or mild character. Those which did occur might well have been occasioned by the strictures of the urethra.

Repeated examinations of the chest and of the sputum for over three years failed to show any evidence of lung tuberculosis, although we realize that the tubercle bacillus may reach the kidney without demonstrable evidences of lung involvement.

At first, owing to the presence of a sinus in the groin, apparently due to a psoas abscess, a tentative diagnosis of Pott's disease with pressure on the cord was made. This diagnosis soon became untenable owing to the absence of other signs of Pott's disease and negative X-rays of the spine.

We have never seen transverse myelitis as a complication of renal sepsis of any sort, much less of renal tuberculosis. A careful search of the recent literature has thrown no light on the subject, while as an accompaniment of renal disease it is not even mentioned. It seems to us that two theories may be advanced to explain the presence of a transverse myelitis, firstly a direct extension of the septic process to the epidural space, and, sec-

ondly, myelitis of toxic origin. The fact that the upper level of the myelitic process was at the tenth or eleventh dorsal segment (seventh or eighth dorsal vertebra) is hardly compatible with a direct extension of the process, unless it were of considerable extent, in the epidural space. This seems unlikely as the process began to clear up after rest in bed, and drainage of the sinus and of the bladder, without any evidence of pus in the bony canal and the cerebrospinal fluid showed no evidence of such a process.

Toxic myelitis is a well-recognized condition although far from common, and the text books tell us but little of its origin. It is occasionally seen during pregnancy, various acute and chronic diseases, probably also as the result of lead or alcohol poisoning, and possibly from exposure to wet and cold. Such a process would tend to clear up quickly as in the case under discussion.

As regards the presence of calculus in a tuberculous kidney all we can say is that it is uncommon. We have been unable to find any statistics in the literature. Morris contents himself with the remark that "it must be remembered that a calculus may be present in a tuberculous kidney." Our own experience in private and hospital cases, combined with that of several of our colleagues with whom we have discussed the subject, has shown that we can muster perhaps a half a dozen cases of true renal calculus complicating tuberculosis. All of us have seen numerous examples of calcified areas in a tuberculous kidney. We are certain, however, that in the case here presented, an actual calculus was present as shown by its shape, its position in the renal pelvis, its smooth surface and its mobility.

So far as we can ascertain this is the first case of inguinal renal fistula ever seen at the Massachusetts General Hospital. We have accordingly made a careful search of the literature and find an almost equal paucity of material.

Henry Morris says that "a (kidney) fistula may open in one of several directions, namely at the loin or groin, into the colon, duodenum, or stomach, into the pleural cavity or lung, or into the peritoneum. Generally there is but a single opening into the cavity of the kidney or ureter, and that is upon the poste-

rior aspect." He further states that there are "many cases on record of urinary fistulae communicating with the kidney and opening externally in the loin or groin through which calculi have been discharged spontaneously or removed by the surgeon," and he also remarks that "tuberculous disease of the kidney is a very pregnant cause of this troublesome condition."

"In a collection of unselected cases of fistula due to renal calculi some of the fistulae followed the bursting of the pyonephrotic kidneys, and others were the result of perinephritic suppuration and the bursting of an extra renal abscess. . . . ." Of those which opened on the external surface of the body only "one or two" opened in the groin.

Sir Frederick Treves mentions renal fistulae in his Manual of Surgery published in 1892, but evidently regards them as a distinct rarity.

Rollin, in his Thèse de Paris, 1889, states that fistulae of renal origin have been described in ancient medical literature, his review of which is most interesting reading. He refers especially, as all of us must, to the monumental work of Rayer, published in 1839, in which a number of cases of spontaneous renal fistulae are recorded and illustrated. Among this number we were unable to find a case of inguinal renal fistula similar to ours. It is obvious, however, that since Rayer's time, thanks to advances in diagnosis and treatment, renal fistulae have become far less common. Rollin was able to collect but thirty-seven cases of more or less contemporaneous date, of which, it is worth noting, only one resembled ours in its manner of opening into the groin.

Chazet, in a Thèse de Paris of 1900, collected twelve cases of renal tuberculosis with fistula formation. He found, as did his predecessors, that such fistulae occurred mostly in the lumbar region in the triangle of Petit. In one case the fistula opened on the inner aspect of the thigh at the level of the lesser trochanter.

Michaud, in his Bordeaux thèse, published in 1912, has reported several cases of transperitoneal renal fistulae and gives a very complete bibliography of the subject in general.

It is obvious from our reading of the scanty literature of the subject and from our careful search for additional material, that

renal fistulae, other than those of traumatic or post-operative origin, have become rapidly and progressively less common, so much so that we have not found reference to a single case in the literature for over twenty years.

When one peruses the literature of an older generation when "renal surgery was the order of the day" (Rollin) one finds many references to renal fistulae either as a preoperative complication or as a postoperative result. It is encouraging, therefore, to realize that owing to the greater tendency of patients to seek earlier relief for their ills, to more accurate and earlier diagnosis, and to better surgery, what was once a not uncommon condition has become practically extinct.

399,

INFILTRATION ANESTHESIA OF THE INTERNAL VESICAL ORIFICE FOR THE REMOVAL OF MINOR OBSTRUCTIONS: PRESENTATION OF A CAUTERY PUNCH[1]

JOHN R. CAULK

St. Louis, Missouri

It has been estimated that 30 per cent of individuals past middle life have prostatic obstruction, yet only 15 per cent seek relief from symptoms of such obstruction. As the public becomes educated to the understanding that urinary disorders are representative of true physical changes and not habit, and furthermore are not natural consequences of age to which they must become reconciled, I dare say the two percentages will approximate. The effectiveness of such education is becoming manifest. It therefore behooves us as surgeons to produce results with minimum risk in order to maintain the confidence of those who consult.

At present the treatment of the gross adenomatous obstruction is practically standardized, that is, through major surgery by either perineal or suprapubic prostatectomy, only a few cases being suitable for less radical measures, such as high frequency or other endo-vesical procedures. Cancer of the prostate offers many problems. Either radium, prostatectomy or the combination of the two are the methods of election; a very few such cases may be treated by radium in association with minor measures.

There still remains an important group of vesical neck obstructions concerning the treatment of which there is no unanimity of opinion, and which offers a field of further investigation and study. I refer to the contracted neck or so called median bar formation. Randall after analyzing 200 autopsy specimens taken as routine found 14 per cent showing various degrees of contracture of the vesical neck or bar formation, a large percentage occurring between the second and fifth decade. Most

[1] Read at the meeting of the American Association of Genito-Urinary Surgeons, Rochester, Minnesota, May, 1920.

of these individuals showed gross changes of obstruction in the bladder and upper urinary tract, although but few had received treatment or had consulted for symptoms of obstruction. Lowsley's analysis of 224 anatomical specimens showed 14.7 per cent due to enlargement of Albarran's glands. The largest percentage of these occurred in the fourth decade. In analyzing 485 clinical cases of prostatic obstruction which have come under my own

Fig. 1. Autopsy Specimen Showing Contracted Vesical Orifice with Bar Formation (after Randall)

observation, 97 have been of this type. In other words, about 20 per cent of all obstructions come under this category. Therefore its significance must appeal to us.

It is with this group of obstruction that we must particularly concern ourselves as it seems to be the open avenue through which we may hope to induce an improvement in general mortality statistics, provided we may establish simple measures, unattended with the dangers of open surgery and productive

of substantial results. With the present day appreciation of the importance of uremia and its preliminary correction before surgery, the judicious selection of cases and modern improvements in technique, we can scarcely hope for much change in the results or in mortality statistics by these major procedures.

Let us not consume time in a discussion of the gross and histological changes of this type of obstruction, as they have been thoroughly studied by Randall, Lowsley and others, but direct our entire attention to the therapeutic correction of such abnormalities. In 1830 Guthrie called attention to this type of orifice as a potent factor in vesical neck obstruction and twenty years later Mercier revived interest in this chapter of prostatism and suggested a novel treatment for its correction. Another period of somnolescence ensued until Young of Baltimore awakened interest by the presentation before this Association of his instrument known as the punch or median bar excisor for the surgical treatment of this disease. In his hands it has proved a very effective method of curing a large percentage of this type of obstruction. Many others have also used this instrument with excellent results. I, personally, have cures lasting over nine years without the slightest return of previous symptoms. It seems certainly true that enough tissue is removed by this method to effect complete relief from obstruction. This operation, however, has not been as popular as it deserves, the chief deterrent being the fear of hemorrhage and absorption. Young himself reports frequent occurrence of hemorrhage and has devised methods for its control, such as coating a retention catheter with kephalin, and instruments for the evacuation of clots.

In the presence of infection there is at times considerable absorption following this operation. I have seen several marked reactions. On account of these complications to the operation Stevens, Bugbee, Lewis and others have proposed simpler methods such as high frequency cauterization and incising the orifice through an endoscope with small cautery blades. While these procedures may be effective in the correction of a few selected cases, they are not applicable or effective in the majority

of these obstructions, since they do not seem to remove sufficient tissue. Furthermore, the procedures have to be repeated and take rather too much time to be acceptable.

The Chetwood galvano-cautery operation has been quite successful in the treatment of this type of obstruction. It is done as a major procedure to accomplish what can be done by simpler means. There are some who believe that partial prostatectomy should be the method of choice and I understand that there are still others who have suggested complete prostatectomy for the relief of this condition.

We must realize that most of the patients belong to the younger group, many of whom do not have severe symptoms, so that major methods should be shunned if possible. Such patients are usually treated by local methods, high dilatations, massage and instillations which occasionally give relief but are seldom of definite, not to speak of ultimate benefit. I have been quite surprised to find in the examination of many of these individuals with early symptoms who have been on local treatment that they were carrying a residual of 3 to 6 ounces.

Believing emphatically that the Young punch operation was the effective way of handling this type of obstruction in that it removed sufficient tissue, but fearing to offer it in many instances as routine on account of the bleeding, pain, absorption and discomfort which it frequently caused, it occurred to me that if the same amount of tissue could be removed by electric cauterization, these complications and occasional dangers might be avoided and the operation made more generally acceptable. For this reason I have taken the liberty of modifying Dr. Young's instrument by placing an electric cautery attachment to the distal part of the inner sheath. Initially I had no intention of presenting this instrument and had it designed only for my personal use. But it has developed so satisfactorily and the results have been so uniformly good, that I felt it might be worthy of presentation before this Association.

This instrument is of the same design as the Young punch, but there are a few modifications which I will describe. The outer sheath has not a fang on the slot in order to hold it in

position, as with the electric cautery the coagulation by burning maintains the instrument in place. The obturator sheath has at its terminus an iridio-platinum blade instead of a knife blade. This blade is about $\frac{1}{4}$ inch in width and of substantial thickness. I tried several smaller blades but they proved entirely unsatisfactory in that they were too frail to stand the pressure and the heat was imperfectly distributed. I have performed 20 punch operations with the present blade and it is still firm and in good condition. The blade is insulated from the main sheath of the instrument by mica plates. At the proximal end of the tube, the current enters through a large contact point with screw attachment, one pole connected with the tube itself, the other

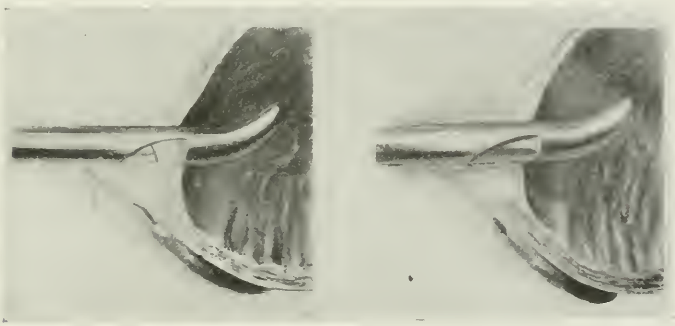


Fig. 2. Views Showing Young's Punch in Operation (after Young)

with a large copper bar brazed to the surface of the tube and insulated with silk and mica. The cord which carries the current from the rheostat to the instrument is of large caliber and practically the same size as the copper bar within the tube.

I wish to explain a few of the essential features of the electric part of this instrument. In order to burn tissue properly and prevent hemorrhage the procedure must be done slowly under low heat. Otherwise the process is about the same as with a cold knife. To do this, we must be able to produce enough heat in the blade to burn the tissue without heating the shaft of the instrument. For this reason the conductors have been made large and of uniform caliber throughout so that they offer

the minimum resistance to the current which is thus brought directly to the only point of increased resistance, the cautery blade. In this way an intense heat may be maintained for a sufficient period of time without heating the instrument. The inner sheath serves as a handle for manipulating the instrument. The burning is best done by a slow rotary motion which is easily regulated by using this handle as a lever. I have put no irrigat-

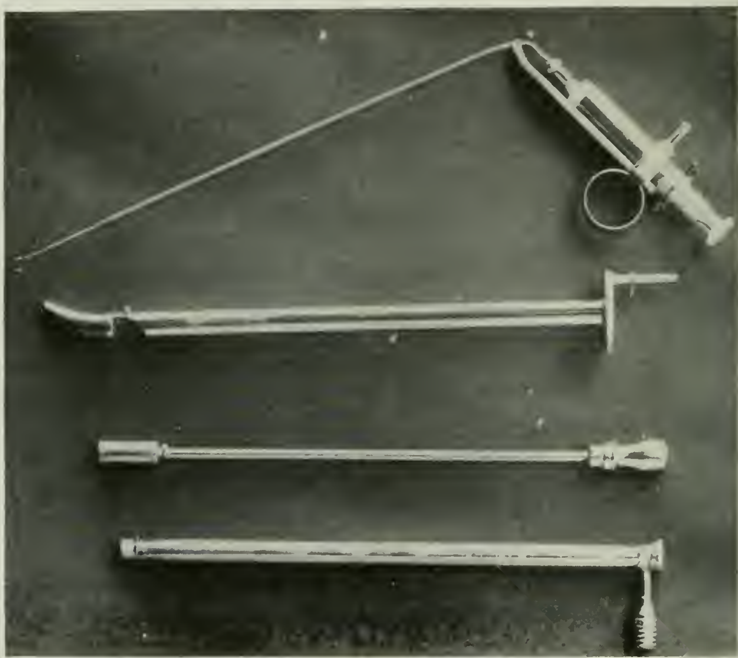


Fig. 3. Cautery Punch Instrument with Syringe for Infiltrating Tissue of the Vesical Orifice with Novocain

ing attachment to the instrument since we do not need dilatation of the orifice and there is much less danger of short circuiting in a dry field.

With the Young punch, the operation can be nicely done under local urethral anesthesia with cocaine or novocain, for it is quickly over and the pain is tolerable. In attempting to remove an obstruction by cautery, however, the procedure must be done

slowly and the ordinary anesthesia is entirely ineffective. For this reason it is essential to have a more profound anesthesia, but since it is our purpose to minimize the risks and hazards of operating, it is most desirable not to subject these patients to general or spinal anesthesia. Sacral anesthesia would be very effective for such operations, but this again falls into the category of major procedures. In observing the obstruction within the grasp of the instrument, it occurred to me that it would be quite simple to infiltrate the tissues of the orifice with novocain through the outer sheath. I accordingly asked Mr. Phillips, an instrument maker, to construct a syringe somewhat on the order of the Geraghty utricle syringe. This syringe has a pistol handle connected with a tube, about a no. 7 French, to the end of which is brazed an iridio-platinum needle. An ordinary Luer syringe is connected with the silver tube at its junction with the handle of the instrument. With this syringe it is perfectly simple under vision to infiltrate the vesical orifice. We have used 1 per cent novocain and one or two 20 mm. syringes usually suffice to produce complete anesthesia.

TECHNIQUE

After washing the urethra and bladder thoroughly and leaving some fluid to be retained, the sheath with its obturator is passed into the bladder, the obturator removed and the fluid evacuated. The orifice is then engaged and the sheath moved around the circumference of the obstruction to be sure it is not trigone, although this is really not necessary. It is usually perfectly simple to discern the orifice with the obstruction engaged in the slot of the instrument. An evacuating tube and cotton pledgets are used to get the field dry. Under reflected light the syringe is passed down the tube and the needle is plunged into the tissue. Considerable pressure is sometimes needed in the very dense obstructions. The needle is gradually pushed through until it comes out on the other side of the obstruction. This is easily appreciated. The instrument is rotated and infiltration is done wherever it is necessary. After a few minutes the cautery blade which has been tested is passed down the sheath, which is held

firmly in the left hand, engaging the obstruction. The current is then applied (with this instrument we use about 150 amperes, which gives the proper heat) and with a rotary motion the obstruction is slowly burned through. When this is completed the current is turned off. The inner tube is removed and the tissue extracted from the blade of the instrument. It is not removed through the inner tube by a forceps as the calibre of the tube is

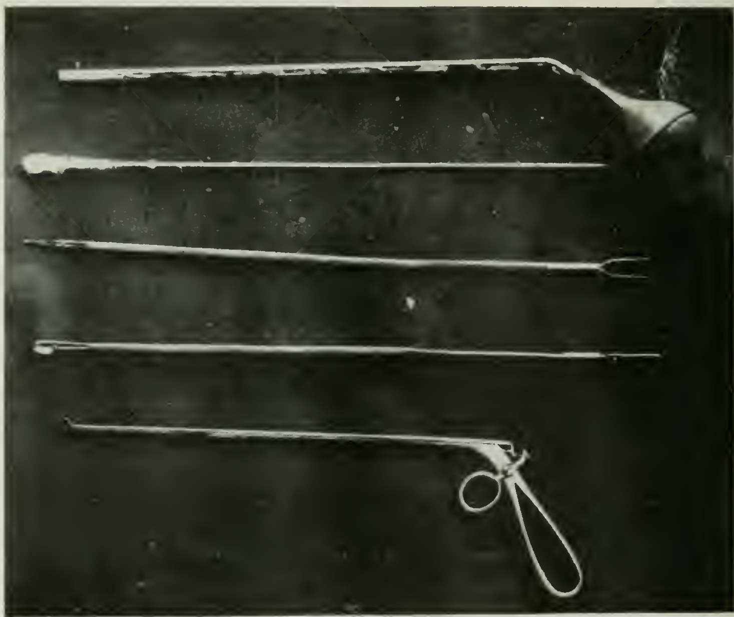


Fig. 4. Aspiration Syringe, Cautery Blades and Forceps for Removing Operative Specimens

encroached upon by the copper bar, and more important is the fact that the tissue is so adherent to the blade through coagulation that it is difficult to detach it. If it is desired to remove pieces on either side of the primary wound, the instrument is rotated to either side and the blade reinserted. I have observed with this instrument which takes a rather large bite, that the midline posterior one is much larger than the others, evidently due to a complete cut through the obstruction allowing lateral retraction

of the tissue. Should there be the slightest bleeding, the obturator tube with blade is reinserted and with very low heat the neck is cauterized. This operation can be done perfectly painlessly, the patient seldom appreciating that it is being executed and they have all remarked that it is less painful than a cystoscopic under local anesthesia.

We have done twenty cases by this method and with the exception of two cases who were suffering with complete retention of urine have not put in a retained catheter. These operations have all been done in the office; most of them have been sent to the hospital for one to three days, several have gone home. We have not encountered a single blood clot and seldom has there

Fig. 5. Showing Needle of Infiltration Syringe

been more than a stained urine, often only a terminal bleeding about the third day, and this very slight. We have had to give but one hypodermic for pain. To my surprise there has not been any large sloughing. Most of the patients have experienced immediate relief, although some have not received the benefit of the operation until the end of a week. There has not been a single chill or reactionary fever following the operation, and two of the patients had high grade uremia with badly infected urines.

All but two of these cases were done on typical median bars either from sclerosis, gland hypertrophy or cancer. The two exceptions were on individuals with lateral lobes; one of them

I wish to call particular attention to. He had had an incomplete perineal prostatectomy nine years ago and had been obstructed since, carrying a high residual urine with paradoxical incontinence. He was put in the hospital for preparatory treatment in anticipation of prostatectomy, as the obstruction was deemed too large to remove otherwise. After three months his improvement was not sufficient to warrant major surgery and it was decided to try the cautery punch In three sittings I removed fourteen pieces of tissue from the orifice and the patient has obtained an excellent result; he now empties his bladder to within one ounce and his general condition is much improved. The other man had really a small sized median lobe, too big to grasp with the punch He also was a bad risk and had a cord lesion. In order to shrink his lobe I had a cautery needle designed with a point about $\frac{3}{4}$ inch long. With this we pierced the lobe in many places and applied cauterization. This caused sufficient shrinkage to allow the punch to be used. The patient had had complete retention, but today empties his bladder entirely. I believe that lobes which are too large to be engaged can often be successfully dealt with in this way.

One patient had a recurrent carcinomatous contracture of the orifice following suprapubic prostatectomy and has been completely relieved of his obstructive symptoms by means of the cautery punch. We have encountered one case of carcinoma of the median bar in a prostate which otherwise seemed nonmalignant. The punch operation has been of great service in post-operative conditions for the removal of contractures and tags. The immediate results of this operation have been most pleasing and gratifying and I see no reason why they should not be as permanent as by the cold cutting, for surely there is sufficient tissue removed to predict a good prognosis.

In analyzing these twenty cases it seems that this operation, owing to its simplicity, its freedom from hemorrhage, absorption and other complications would offer itself as the method of choice for the group of prostatic obstructions due to median bar formations or contractures of the vesical neck, and since it should be attended with a negligible mortality, it commends itself as a means of reducing the gross death rate of prostatic surgery.

THE ACTION ON THE GONOCOCCUS OF SODIUM OLEATE, ALONE AND IN COMBINATION WITH OTHER DRUGS

DAVID M. DAVIS AND ERNEST O. SWARTZ

From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Maryland, with the Aid of Funds Granted by the United States Interdepartmental Hygiene Board for the Study of the Prevention and Cure of Venereal Diseases.

I. INTRODUCTION

The bacteriolytic power of soap has been extensively investigated as a result of the demonstration that soaps are largely responsible for the bacteriolytic properties of inflammatory exudates. This action of soap is a specific one, being marked with certain species of organisms, and practically absent with others. Its powerful effect on pneumococci led us to the assumption that similar results might be observed with the gonococcus, an organism having certain characteristics in common with Fraenkel's coccus.

II. HISTORICAL

Lamar (1) has studied extensively the action of soaps on pneumococci. The observation by Welch (2) that pneumococci are dissolved by pneumonic exudate, was followed by that of Klotz (3), that this lytic power is due largely to soaps, and that of Noguchi (4) that soaps are bactericidal for typhoid, anthrax, and dysentery organisms. Lamar found, as expected, that soap would dissolve and kill pneumococci, but in addition he noted that treatment with sub-lethal concentrations of soap would so change the organisms that they were readily killed and dissolved by anti-pneumococcic serum. This serum shows no bactericidal or bacteriolytic properties for untreated pneumococci. The soaped cocci are not, however, more easily phagocyted than untreated ones. Soap has practically no effect on staphylococci.

In the presence of serum or other proteins, the bactericidal and bacteriolytic power of soap is inhibited. According to Klotz (3), this is due to the formation of a soap-albumen complex, which does not have the properties of soap. v. Liebermann (5) noted that the addition of oleic acid to such a mixture restored to it hemolytc activity, and later he and v. Fenyvessy (6) found that boric acid or any other weak acid had the same effect. Noguchi (4) observed that, while a soap-normal serum mixture was inactive, in some cases the addition of soap increased the effectiveness of an immune serum.

Lamar utilized boric acid in his soap-serum mixtures, and found that it largely did away with the inhibition of the action of the soap by the serum. With the aid of mixtures of soap, boric acid and immune serum, injected intravenously, he was able to save mice which had been inoculated with lethal doses of virulent pneumococci. These mixtures, however, have not been found effective in the treatment of human pneumonia. It seems that much greater promise is held out, at least in the present incomplete state of our knowledge concerning the activity of soap in the normal and pathological states of the body, by the use of soaps in localized infections, where application can be made direct instead of through the medium of the blood, and where conditions can be more accurately controlled.

Bond (7) used mixtures of acriflavine and soap as an ointment for infected wounds. He apparently selected soap merely as a menstruum. Berkeley, Bonney and Browning (8) described proflavine oleate, also used to make an ointment for local application to wounds. They state that the proflavine oleate is comparatively insoluble in water, but that a sufficient quantity will dissolve in serum to confer upon it antiseptic properties. This slow solubility of the antiseptic, together with the non-adhesive character of the ointment, are given as its advantages. No mention is made of the specific bactericidal or bacteriolytic properties of oleates.

The use of soap and water has always been recommended in the prophylaxis of venereal disease. Reasoner (9) found that strong soap solutions, the strength of which is not stated, would

immediately destroy the motility of spirochaetes, and later dissolve them. Moore (10) performed experiments which showed that soap and water was an effective preventive of chancroidal infection, while calomel ointment alone had no such effect.

Since the effect of soap on gonococci might be expected to be analogous to that on pneumococci, we decided to determine the extent of this effect, and also any enhancing effect which soap might have upon the germicidal power of other drugs for the gonococcus.

III. METHODS

The method used is that described by us in a recent paper (11). Briefly, it is as follows:

1 cubic centimeter of the emulsion is pipetted into a centrifuge tube of diluted drug. The tube is placed in the water bath at 37.5°C. for eighteen minutes. At the end of this time, it is centrifuged at high speed for two minutes. The supernatant fluid is poured off, and a quantity of salt solution pipetted in. This makes the complete time of action of the drug 20 minutes. The tube is then centrifuged a second time, and the wash fluid poured off. The gonococci settle readily in the centrifuge, and form a compact mass at the tip of the tube, which can be transferred almost en masse, to a tube of fresh media. This is corked and incubated, as described by Swartz (12). It is our custom to inoculate, after seven days, all tubes upon which no growth has occurred, with fresh cultures of gonococci. If they develop, we assume that enough of the drug has not been carried over to the test-medium to prevent growth. The final growths are examined microscopically with the Gram stain. None of our strains of gonococci grew upon plain media.

IV. RESULTS

The first experiments were performed with sodium oleate alone, in varying dilutions. The gonococci were suspended in Locke's solution. The sodium oleate used was Sodium Oleate-Merck, neutral powder. The results are given in table 1.

By this technique, the germicidal value was low. The mixture of sodium oleate and Locke's solution was cloudy, owing

to a precipitate. This was undoubtedly the insoluble calcium oleate. Therefore, in succeeding series, 0.85 per cent sodium chloride solution was substituted for Locke's solution. The results of such a series are shown in table 2.

TABLE 1

Sodium oleate—Gonococci suspended in Locke's solution

GONOCOCCI	STRENGTH OF SOLUTION												
	1:50	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1500	1:2000	1:3000	1:5000	Control Locke's
24-hour reading	0	0	0	+	+	+	+	+	+	+	+	+	+	+
48-hour reading	0	0	0	+	+	+	+	+	+	+	+	+	+	+
72-hour reading	0	0	0	+	+	+	+	+	+	+	+	+	+	+
Tubes reinoculated:														
24-hour reading..	+	+	+											
48-hour reading..	+	+	+											

C = Control tube; + = growth of gonococcus; 0 = no growth of gonococcus.

TABLE 2

Sodium oleate—Gonococci suspended in 0.85 per cent NaCl solution

GONOCOCCI	STRENGTH OF SOLUTIONS										
	1:100	1:250	1:500	1:750	1:1000	1:1500	1:2000	1:3000	1:5000	1:10000	Control NaCl
24-hour reading..............	0	0	0	0	0	+	+	+	+	+	+
48-hour reading..............	0	0	0	0	0	+	+	+	+	+	+
72-hour reading..............	0	0	0	0	0	+	+	+	+	+	+
Tubes reinoculated:											
24-hour reading..........	+	+	+	+	+						
48-hour reading..........	+	+	+	+	+						

C = Control tubes; + = growth of gonococcus; 0 = no growth of gonococcus.

In the absence of calcium, the oleate shows a definite germicidal value for the gonococcus. The emulsions used above, however contained a small quantity of uncoagulated protein derived from the culture media, and in order to eliminate the inhibitory effect

of this on the sodium oleate, an experiment was performed in which the gonococci were washed several times in 0.85 per cent sodium chloride solution before being suspended in the same. Table 3 shows the result.

Evidently, there had been a serum inhibition in the previous experiment. The effect of boric acid in eliminating the inhibitory effect of serum was tested by repeating the experiment shown in table 2, with the addition of boric acid to each tube in a strength of 0.5 per cent. Solutions of boric acid in distilled water of the desired strength produced cloudiness in the sodium oleate solutions. Tests showed that the boric acid solutions had a reaction of pH 3.0. When neutralized with $\frac{N}{10}$ NaOH, using dibrom-

TABLE 3

Sodium oleate—Gonococci washed and suspended in 0.85 per cent NaCl solution

GONOCOCCI	STRENGTH OF SOLUTIONS									
	1:50	1:100	1:200	1:300	1:400	1:600	1:800	1:1000	1:2000	Control NaCl
24-hour reading	0	0	0	0	0	0	0	0	0	+
48-hour reading	0	0	0	0	0	0	0	0	0	+
7-day reading	0	0	0	0	0	0	0	0	0	+
Tubes reinoculated:										
24-hour reading	+	+	+	+	+	+	+	+	+	+
48-hour reading	+	+	+	+	+	+	+	+	+	+

C = Control tube; + = growth of gonococcus; 0 = no growth of gonococcus.

thymolsulphon-phthalein as an indicator, they no longer gave the precipitate with oleate. As a consequence, we had a solution of boric acid containing some sodium borate, but it gave the desired results. Lamar does not mention this reaction between boric acid and oleate. Table 4 shows this experiment.

The addition of boric acid makes the sodium oleate about three times as effective under the conditions of our experiment.

Experiments were performed to determine the percentage of boric acid most advantageous for this purpose. Variations through a fairly wide range of concentrations made no apparent difference in the growth, and therefore 0.5 per cent was used throughout the work.

The effect of sodium oleate in enhancing the germicidal power of other drugs was tested by adding to the different dilutions a constant sub-lethal quantity of sodium oleate, together with enough boric acid to produce a concentration of 0.5 per cent in the test mixture. Trials were first made with 1:16,000 oleate, but it was found that this had little effect. Consequently, 1:8000 was adopted. The experiment was performed as follows:

Dilutions of the drug were made up, with aseptic precautions, to be five times as strong as the concentration desired in the test mixture. One-half cubic centimeter of each was placed in

TABLE 4

Sodium oleate—Gonococci suspended in 0.85 per cent NaCl solution, 0.5 per cent boric acid in each tube

GONOCOCCI	STRENGTH OF SOLUTIONS											
	1:100	1:250	1:500	1:750	1:1000	1:1500	1:2000	1:3000	1:5000	1:10000	Control NaCl	Control, NaCl + boric acid
24-hour reading........	0	0	0	0	0	0	0	0	+5*	+10*	+	+
48-hour reading........	0	0	0	0	0	0	0	0	+5*	+10*	+	+
7-day reading..........												
Tubes reinoculated:												
24-hour reading....	+	+	+	+	+	+	+	+				
48-hour reading....	+	+	+	+	+	+	+	+				

C = Control tube; + = growth of gonococcus; 0 = no growth of gonococcus.
* Few colonies. The figures indicate the number of colonies.

a sterile cotton stoppered centrifuge tube. To each tube of the series was added 0.5 cc. of 1:1600 sodium oleate and 0.5 cc. 2.5 per cent boric acid. Finally 1 cc. of gonococcus emulsion was put in. It will be seen that this produced, in the whole mixture, concentrations of 1:8000 for sodium oleate, and 0.5 per cent for boric acid, and the desired dilution of the test-drug. From this point on, the technique was as described above. The test period was twenty minutes. Three controls were always made, one containing 1.5 cc. of distilled water and 1 cc. of emulsion; the second containing 1.5 cc. of 0.85 per cent NaCl solution

and 1 cc. emulsion; and the third containing 0.5 cc. of distilled water, 0.5 cc. of 1:1600 sodium oleate, 0.5 cc. 2.5 per cent boric acid, and 1 cc. of emulsion. All the controls always showed growth, and the last proved that the 1:8000 sodium oleate and 0.5 per cent boric acid alone would not kill the gonococci.

Such an experiment, with Mercurochrome-220, is shown in table 5.

TABLE 5

Sodium oleate 1:8000—Gonococci suspended in 0.85 per cent NaCl solution; Mercurochrome—220 varying; boric acid 0.5 per cent

GONOCOCCI	STRENGTH OF MERCUROCHROME-220									
	1:2000	1:4000	1:8000	1:16000	1:32000	1:64000	1:128000	Control H_2O	Control NaCl	Control boric + oleate
24-hour reading	0	0	0	0	0	0	+	+	+	+
48-hour reading	0	0	0	0	0	0	+	+	+	+
7-day reading	0	0	0	0	0	0	+	+	+	+
Tubes inoculated:										
24-hour reading	+	+	+	+	+	+				
48-hour reading	+	+	+	+	+	+				

C = Control tube; + = growth of gonococcus; 0 = no growth of gonococcus.

The addition of this sub-lethal quantity of sodium oleate increased the germicidal value of Mercurochrome-220 about four times. (In this connection attention should be called to the fact that the germicidal power of solutions of Mercurochrome-220 diminishes on standing (13). These tests were made with freshly prepared solutions.) The same technique was used in a series of tests to determine the effect of adding 1:8000 sodium oleate to various other drugs. The results are shown in table 6.

The solutions of the silver compounds and chlorazene were freshly made from material purchased in the open market. The phenol solutions were made from the chemically pure drug in the laboratory. The sample of tricresols was a product redistilled between 195° and 205°C. which was furnished by Dr. R. T. Devereaux of the Mulford Company, to whom we are much indebted. It was about two months old, had been kept in

brown glass in the cold, and showed only a very slight brownish-yellow discoloration. For potassium mercuric iodide, equal weights of mercuric iodide C. P., and potassium iodide, C. P. were mixed, and the dilutions calculated for their content of the double salt. The excess of potassium iodide is necessary to retain the double salt in solution. The drugs indicated by number preceded by "M" belong to the Mercurochrome series, developed in this laboratory. Number 220 is the drug described by Young, White and Swartz (14). The others are described in

TABLE 6

GONOCOCCI	ALONE		WITH SODIUM OLEATE 1:8000 AND BORIC ACID 0.4 PER CENT	
	Kills	Grows	Kills	Grows
Silvol	1:400	1:800	1:2000	1:4000
Cargentos	1:800	1:1000	1:2000	1:4000
Argyrol	1:800	1:1600	1:2000	1:4000
Protargol	1:400	1:800	1:2000	1:4000
Phenol	1:200	1:400		1:250
Tricresols	1:800	1:1600	1:1000	1:2000
Potassium mercuric iodide	1:40000	1:80000	1:80000	1:160000
Chlorazene	1:3200	1:6400	1:12000	1:24000
M-205	1:1000	1:2000	1:1000	1:2000
M-220	1:16000	1:32000	1:64000	1:128000
M-226	1:32000	1:64000	1:128000	1:256000
M-230	1:8000	1:16000	1:20000	1:40000
M-235	1:16000	1:32000	1:30000	1:60000
C-244	1:3200	1:6400	1:24000	1:48000
C-245	1:64000	1:128000	1:64000 1:120000	1:128000
C-246	1:51200	1:80000	1:40000	1:80000

another paper by White, Swartz, and Davis (15). Those indicated by numbers preceded by "C" are colorless drugs belonging to a new series of organic mercurial compounds also developed in this laboratory. Further details are given in the above-mentioned paper. Also solutions were freshly made for the tests.

In all the experiments with oleate, the gonococci showed markedly its effect, being changed to a translucent, slippery mass quite different from the usual appearance in the tip of the

centrifuge tube. This occurred even in weak dilutions, where good growths were obtained from these altered gonococci.

Other authorities state that sodium oleate has little effect on B. coli and S. aureus. Tests carried out by us confirm this observation, since neither organism was killed by exposure to 2 per cent sodium oleate for twenty minutes, using the same technique as for gonococcus.

DISCUSSION

It will be seen from table 6 that sodium oleate is much more effective in increasing the germicidal power for the gonococcus of certain drugs than of others. With phenol and the tricresols the increase is slight; with potassium mercuric iodide, Mercurochrome-235 and Mercurochrome-230 somewhat greater; and with the silver compounds, chlorazene, Mercurochrome-220, Mercurochrome-226 and C-244 of a still higher order. In the case, however, of Mercurochrome-205, C-245 and C-246, there is no increase whatever. The explanation for Mercurochrome-205 is not apparent, but with these "C" compounds, may be a matter of reaction. These substances differ from the Mercurochromes, which are slightly alkaline, in having slightly acid solutions (about pH 5.8). The solutions of sodium oleate are slightly alkaline, ranging from pH 8.2 for a 1:8000 solution to pH 8.6 for a 1:16,000 solution. Solutions of sodium oleate have a distinct buffer value. This change in reaction may prevent any improvement in the action of these "C" compounds by sodium oleate, but cannot be regarded as a general rule, since the action of acriflavine which has acid solutions (pH 5.7) is distinctly increased by the addition of 1:8000 sodium oleate (16).

Sodium oleate solutions can be borne in the urethra without symptoms of irritation up to a strength of 1 per cent. These experiments suggest the use of a mixture of sodium oleate and boric acid as an adjuvant to other drugs in the treatment and prophylaxis of gonorrhea. In the case of irrigations, the soap would assist the cleansing action, in addition to its germicidal or opsonic value. In prophylaxis, the action of soap should be taken advantage of within the urethra as well as externally, where its value has long been taught.

CONCLUSIONS

1. Sodium oleate has a definite germicidal value for the gonococcus.

2. This value is increased, where uncoagulated protein is present, by the addition of boric acid.

3. The presence of small, sublethal quantities of sodium oleate increases the germicidal action of many drugs against the gonococcus. With others it is without effect.

4. Sodium oleate with boric acid is suggested as an adjuvant to other drugs in the treatment and prophylaxis of gonorrhea.

REFERENCES

(1) Lamar, R. V.: Chemo-immunological studies on localized infections. Jour. Exp. Med., 1911, xiii, January 5, no. 1, and March 1, no. 3.

(2) Welch, W. H.: Report on Diplococcus pneumoniae. Johns Hopkins Hospital Bull., 1890, i, no. 6, 73.

(3) Klotz, O.: Studies upon calcareous degeneration. Jour. Exp. Med., 1905, vii, 633.

(4) Noguchi, Hedeyo: Über Gewisse Chemische Komplimentsubstanzen. Biochem. Ztschr., 1907, vi, 327.

(5) von Lieberman, L.: Über Hamagglutination und Hamalolyse. Biochem. Ztschr., 1907, iv, 25.

(6) Lieberman and Fenyvessy: Ztschr. f. Immunitatsforchung, 1909, ii, 436.

(7) Bond, C. J.: Acriflavine paste as a dressing for infected wounds. Brit. Med. Jour., 1917-11-6.

(8) Berkeley C., and Bonney, V.: Proflavine oleate in the treatment of open wounds. Brit. Med. Jour., i, 152, February 8, 1919.

(9) Reasoner, M. A.: The effect of soap on Treponema pallidum. Jour. Amer. Med. Assn., lxviii, no. 13, p. 973, March 31, 1917.

(10) Moore, J. E.: The diagnosis of chancroid and the effect upon its incidence in the American Expeditionary Force of prophylaxis. Jour. Urology, iv, no. 2, 169.

(11) Davis, D. M., and Swartz, E. O.: The testing of germicidal substances against the Gonococcus. Forthcoming paper in the Journal of Infectious Diseases. 1921.

(12) Swartz, E. O.: A new culture method for the gonococcus. A report of experimental studies. Jour. Urology, August, 1920, iv, no. 4, 325-345.

(13) Swartz, E. O., and Davis, D. M.: Action on the gonococcus of Mercurochrome-220. Forthcoming publication.

(14) Young, H. H., White, E. C., and Swartz, E. O.: A new germicide for use in the genito-urinary tract: Mercurochrome-220. Jour. Amer. Med. Assn., November 15, 1919, lxxiii, 1483.

(15) White, E. C., Swartz, E. O., and Davis, D. M.: Action on the gnococcus of certain organic compounds of mercury. Forthcoming publications.

(16) Personal observations.

HEXAMETHYLENAMIN: ITS QUANTITATIVE FACTORS IN THERAPY

ALFRED T. SHOHL AND CLYDE L. DEMING

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

Hexamethylenamin, under the trade name "Urotropin," is one of the drugs most frequently used both for prophylaxis and treatment in genito-urinary infections. It is non-toxic, stable, pure, cheap, and can be taken by mouth in large doses. It is excreted unchanged by the kidney, and becomes active in the urine through the liberation of formaldehyde. Hexamethylenamin itself is not germicidal; formaldehyde is a powerful germicide. The splitting of hexamethylenamin into formaldehyde and ammonia occurs only in acid solutions or in acid urines. Because of its many advantages, it has often been called our best urinary antiseptic.

This fairly summarizes our knowledge of this drug. There are still many gaps in our understanding of its action and the best method to administer it. The importance of these problems is such that Dr. Hugh H. Young suggested their reinvestigation. Our knowledge, though in general resting upon a firm experimental basis, lacks the quantitative data necessary to determine actual procedure.

The problems we have studied are:

1. The strength of formaldehyde necessary to kill and to inhibit growth of B. coli in urine. The concentration of formaldehyde, temperature, and time of action must be the same as those found in the body.
2. The methods of measuring free formaldehyde in the urine.
3. The method of measuring the acidity of the urine.
4. The amount of formaldehyde formed from hexamethylenamin at varying acidities.

5. The amount of formaldehyde formed in twenty-four hour urine standing twelve hours.

6. The amount of hexamethylenamin excreted in the urine and the loss of hexamethylenamin in the stomach.

7. Fluid intake and its effect on the acidity of the urine.

8. Methods for increasing the acidity of the urine.

9. Germicidal action of formaldehyde in the presence of ammonia in alkaline solutions.

10. The antiseptic strength of urine after the administration of hexamethylenamin.

1. The strength of formaldehyde necessary to kill and to inhibit growth of B. coli in urine. The ideal drug would kill all the organisms in a short time without harm to the body, but any change that can be made in the life cycle of the bacterium may be used to the advantage of its host. The basic principles in antisepsis have recently been reviewed by D. M. Davis and E. O. Swartz in their studies on the effect of germicides on gonococci. Modern researches show that the laws of antisepsis are subject to mathematical statement, if the conditions as to concentration of the drug, time, temperature and acidity are fixed.

At a given temperature and time varying concentrations of a drug produce different degrees of toxicity. These stages of injury to the organism may be classed: (1) Abnormal metabolism, (2) cessation of function, (3) inhibition of growth, (4) cessation of growth, (5) decreased immunity to other agents, (6) partial killing, (7) complete killing.

Researches on the concentration of formaldehyde and its killing power are of course plentifully found in the literature. Most of the work has been done by adding formalin to the culture media and then inoculating with various organisms. At best this gives the concentration which inhibits growth. The time element so important in this problem is entirely lacking.

The factors which we have taken into account are the concentration of formaldehyde which may be obtained in the body after giving hexamethylenamin, the time, the temperature, the medium and the acidity. We chose B. coli as our test organism because this is the commonest invader of the genito-urinary tract.

The time during which a germicide acts is of equal importance with its concentration. Chick has shown that the longer the germicide of a given strength acts, the greater will be the killing power, for the total effect is the product of the concentration and the time. If the urine is voided every four hours, two hours is the average time it remains in the bladder. Our early experience showed that with the therapeutic use of hexamethylenamin we could not expect killing of all but only a part of the organisms in two hours.

The temperature of the medium is of great importance in studies of antiseptics. Accurate studies by Chick and others have shown that the germicidal power increases with the temperature. In addition the temperature effects the rate of growth of the organisms. Therefore, we did all our work at body temperature, 37°C.

The medium is important also. In a search of the literature we have been able to find no complete studies made on urine. Urine exhibits different properties from water or salt solution. It requires much higher concentrations of the antiseptic to kill the organisms, as has been shown by E. G. Davis. Urine differs from other culture media also in relation to its effect on growth of organisms; for Shohl and Janney showed that in urine there was a protracted "lag." The organisms do not begin to multiply for four hours.

The acidity of the medium is doubly important in this case. It affects the rate of growth. The organisms multiply most rapidly near neutrality, pH 7.0. Solutions which are more acid or more alkaline give poorer growth and at pH 4.6 and pH 9.6 all growth ceases. The rate of transformation of hexamethylenamin into ammonia and formaldehyde is directly dependent upon the acidity. The reaction does not take place in alkaline solutions and becomes more rapid the greater the acidity.

Experimental. Methods of obtaining sterile urine, of diluting, plating and counting the organisms, and of measuring and changing the acidity of the urine have been previously described by Shohl and Janney. Dilutions of formaldehyde were made from a solution of formalin and kept as a stock solution of 1:1000,

from which dilutions were made. The stock solution was checked by the Jorissen-Collins-Hanzlik method and also by the peroxide and iodine methods.

To 10 cc. samples of freshly voided sterile urine in test tubes we added respectively 3.0, 1.5, 0.75, 0.375 cc. of 1:1000 formaldehyde; also 1 cc. of a dilution of twenty-four-hour bouillon culture of B. coli containing approximately 50,000,000 organisms, and sterile water to bring the contents of each tube to 15 cc. The tubes were kept at 37°C. in a water bath. At intervals 1 cc. samples were removed and diluted with sterile salt solution inoculated into agar and poured into Petri dishes. The organisms were counted after incubating for forty-eight hours.

TABLE 1

Per cent of organisms killed in urine at 37°C. by formaldehyde

	CONCENTRATION OF FORMALDEHYDE			
	1:5000	1:10,000	1:20,000	1:40,000
15 minutes	67	20	5	0
1 hour	86	60	35	0
2 hours	88	80	50	20
24 hours	100	100	0	0

The concentration of formaldehyde is indicated by the fraction at the top of the columns. The per cent killed was calculated with reference to the number of organisms growing in urine containing no formaldehyde. Control urine pH 5.6

The results given in table 1 show that, in urine, at body temperature, a concentration of formaldehyde 1:5000 to 1:10,000 kills 80 to 88 per cent of the organisms in two hours, and 100 per cent in twenty-four hours. A concentration of 1:20,000 will kill 50 per cent in two hours, but after this time the organisms grow normally, and in twenty-four hours reach the same number as is reached by the control. Thus, in the body we cannot expect complete germicidal action in a single dose or doses sterilans magna. The treatment must be continued to obtain sterilization, 1:10,000 is sufficient to give partial killing; 1:20,000 is of doubtful value; and higher dilutions, 1:40,000, cause only a temporary inhibition of growth.

2. *The method of measuring free formaldehyde in the urine.* The methods which measure free formaldehyde without decomposing the hexamethylenamin are for clinical purposes practically reduced to three, Rimini-Burnam, the Dunning, and the Jorissen-Collins-Hanzlik. The first test is made with phenylhydrazin hydrochloride and sodium nitroprusside. It is only roughly quantitative. Though Hinman has tried to make this more exact, it has serious drawbacks. The colors are inconstant, and the materials unstable; so that fresh solutions must be made up for each test.

The Dunning test is more sensitive (he claims 1:50,000,000). It is made by phenylhydrazin (base, not hydrochloride) and alkali. This test in our hands was more satisfactory than the former, but there are several objections to it also. The colors take ten to fifteen minutes to develop, and later all become equally intense, so as to necessitate running a set of known concentrations of formaldehyde with each test. Turbidity is also an objectionable feature. Several modifications were attempted with some improvement, but none in our experience was equal to the Jorissen method as modified by Collins and Hanzlik. This method gives accurate and rapid determinations by the use of phloroglucin in alkali. The amount can be quantitated by reading against fairly permanent colored solutions made from dilutions of congo red and methyl orange. We have found that in urine accurate and rapid determinations can be made without filtering. If 10 to 20 cc. samples are diluted to 50 cc., the precipitate of calcium phosphate forms so slowly as not to interfere with the reading. Second, we have made better readings by the compensation method which should be applied in all such colorimetric work. The principle is to neutralize the color of the urine. Collins and Hanzlik suggest adding urine to the standards. Under these conditions, they must be made up fresh for every specimen. A much easier procedure is to take two specimens of urine, one of which is treated with phloroglucin and alkali, as above, and the other simply diluted with water. If one places the diluted urine behind the standard, and a tube of clear water behind the sample, the extraneous color

of the urine is present in each set, and the color is thus compensated.

For completeness, the method of standardizing the solutions of congo red is quoted from Collins and Hanzlik:

1.7616 gm. of $K_2Cr_2O_7$ by titration against alkali (roughly about 30 cc. of a 5 % solution) and 11.5537 gm. of absolute H_2SO_4 (about 7 cc. concentrated) are mixed and diluted to the mark in a 50 cc. Nessler tube with a column of 12 cm. This is equivalent to 50 cc. of 1: 100,000 absolute formaldehyde, or 50 cc. of a congo standard 1: 100,000 which contains 0.000625 gm. of the original dry congo red, or 2.5 cc. of, 0.025%. It is only necessary therefore to prepare a proper mixture of $K_2Cr_2O_7$ and H_2SO_4, and when an unknown congo solution is standardized against this, the quantity used will contain 0.000625 gm. of congo. The strong dilution can then be diluted or made accordingly, the standard dilutions from this to be equivalent to the different concentrations of formaldehyde.

Standard mixtures of congo red and methyl orange

CONCENTRATION OF FORMALDEHYDE	PERCENTAGE CONCENTRATION OF FORMALDEHYDE	CONGO RED 0.025 PER CENT	METHYL ORANGE 0.01 PER CENT
		cc.	*cc.*
1:20,000	0.005	20.0	0
1:30,000	0.0033	11.0	0
1:40,000	0.0025	9.0	0
1:50,000	0.002	8.0	0
1:60,000	0.0016	5.0	0
1:80,000	0.00125	4.0	0
1:100,000	0.0010	2.5	0
1:200,000	0.0005	0.85	0.40
1:250,000	0.0004	0.65	0.35
1:500,000	0.0002	0.25	0.18
1:750,000	0.00014	0.20	0.15
1:1,000,000	0.00010	0.13	0.10

(From Collins and Hanzlik, 1916)

The procedure is to take 10 to 20 cc. of urine in a 50 cc. 12 cm. Nessler tube. Dilute with water until the solution has nearly reached the graduated mark. Add 1 cc. of 1 per cent phloroglucin in 10 per cent sodium hydrate, and dilute to the mark. Compare the color with standards of congo red, made and

standardized as described by Collins and Hanzlik. The color develops to its maximum intensity in about 3 minutes. Compare the colors by the compensation method and read off directly in terms of concentration of free formaldehyde.

This method is so simple that it should be used clinically for the intelligent supervision of treatment.

3. Method of measuring the acidity of the urine. Of equal importance with the measurement of the formaldehyde content is the measurement of the acidity of the urine, for upon this the amount of formaldehyde depends. In modern terms acidity is determined by the amount of the ionized hydrogen in solution. In measuring acidity, one measures the number of hydrogen ions per liter or the hydrogen ion concentration per liter. The hydrogen ion concentration of pure distilled water is 0.0000001 gram per liter, or 10^{-7} grams per liter. A solution in acid when the $(H)^+$ (hydrogen ion concentration) is greater than 10^{-7}, or alkaline when the $(H)^+$ is less than 10^{-7}. Instead of writing out the actual numbers or using such an expression as 1×10^{-7}, it is more usual to write this with the symbol pH, thus pH 7.0. This is the exponent of the number to the base ten expressed as a whole number with the minus sign omitted. According to this terminology, the smaller the pH number, the more acid is the solution. Thus pH 7.0 represents true neutrality and pH 4.7 the most acid, and pH 8.7 the most alkaline urine observed.

The method for measuring acidity is based upon the property of indicators to show different colors at different pH values. All that is required is a set of solutions the pH of which is accurately known, and the proper indicators. The first to apply this method in measuring the acidity of the urine were Henderson and Palmer and Höst. Since their original methods, there have been some improvements. The standard or known solutions and indicators we have found most satisfactory are those of Clark and Lubs.

The indicators are made as follows:

For phenolsulphonphthalein make a 0.02 per cent solution of its sodium salt in distilled water. The solution used for renal function tests contains 6 mgm. per cc. Therefore 1 cc. of this solution diluted to 30 cc. gives the proper solution. Use 1 cc.

for each 120 cc. flask containing either the standard or the sample. Use dibrom-cresol in a 0.04 per cent solution. Make methyl red by dissolving 0.1 gram in 300 cc. of alcohol and diluting to 500 cc. with distilled water.

The composition of the standards is shown in table 2.

TABLE 2

Standard solutions and indicators

INDICATOR	pH		N/5 NaOH	
			cc.	
Methyl red	4.6	50 cc. M/5KH phthalate	12.15	Make up to 200 cc.
	4.8	50 cc. M/5KH phthalate	17.70	
	5.0	50 cc. M/5KH phthalate	23.85	
	5.2	50 cc. M/5KH phthalate	29.95	
	5.4	50 cc. M/5KH phthalate	35.45	
	5.6	50 cc. M/5KH phthalate	39.85	
Dibrom o-cresol sulphon phthalein	5.8	50 cc. M/5KH phthalate	43.00	
	6.0	50 cc. M/5KH phthalate	45.45	
	6.2	50 cc. M/5KH phthalate	47.00	
	6.2	50 cc. $M/5KH_2PO_4$	8.60	
	6.4	50 cc. $M/5KH_2PO_4$	12.60	
	6.6	50 cc. $M/5KH_2PO_4$	17.80	
Phenol sulphon phthalein	6.8	50 cc. $M/5KH_2PO_4$	23.65	
	7.0	50 cc. $M/5KH_2PO_4$	29.63	
	7.4	50 cc. $M/5KH_2PO_4$	39.50	
	7.8	50 cc. $M/5KH_2PO_4$	45.20	

These solutions can be preserved with a few drops of thymol-chloroform or toluol to prevent the growth of molds.

The procedure for measuring the acidity of the urine is as follows:

Take 10 cc. of the standard solution in 120 cc. clear glass flask. Add 1 cc. of indicator methyl red for pH 4.6–5.6, 1 cc. of dibrom-cresol sulphonphthalein for pH 5.6–6.6, and 1 cc. phenol sulphon-phthalein for pH 6.6–8.2. Fill to the top with distilled water.

Take 10 cc. of urine in a flask of the same size and shape. Add 1 cc. of the indicator solution. (It is convenient to use dibrom-cresol first; if the specimen is more acid than pH 5.6, a second test is made with methyl red; if more alkaline than

pH 6.6, with phenolsulphonphthalein.) Dilute to the same volume as the standard. The standard which the color of the sample most nearly matches represents the hydrogen ion concentration of the urine.

4. The amount of formaldehyde formed from hexamethylenamin at varying acidities. Acid converts hexamethylenamin into formaldehyde and ammonia. This has been pointed out by Jordan (1910), Hinman (1913), and in more exact terms by Smith (1913), and Hanzlik and Collins (1913). The acidity is the basic condition for the transformation. Hinman was able to show that by titrations with alkali to the end point of phenolphthalein, he could predict those urines which would show considerable amounts of formaldehyde. The exceptions to this rule he was unable to explain. Smith and Hanzlik and Collins showed that the liberation of formaldehyde was dependent upon the true acidity or hydrogen ion concentration of the solution. Those solutions which were more alkaline than pH 7.0 gave no formaldehyde. Those which were acid gave free formaldehyde. No one has attempted to show quantitatively how much formaldehyde is produced for a definite acidity.

We have come to the conclusion that in a given solution, the amount of hexamethylenamin which is unchanged and amounts of formaldehyde and ammonia which are free depend upon the hydrogen ion concentration. There is a definite equilibrium for each point on the hydrogen ion scale. The final amounts are not formed immediately; the reaction progresses slowly until the equilibrium is established.

The most direct proof is to add a known amount of hexamethylenamin to a buffer solution of known hydrogen ion concentration. One gram of hexamethylenamin gives 1.28 grams of formaldehyde. To 5 cc. portions of the standard solutions of phthalates and phosphates we added 10 cc. of hexamethylenamin of such strength, 1:600, that if it were all converted into formaldehyde, it would give a solution of 1:470.

The hydrogen ion concentration is expressed in terms of pH; pH 4.6 is the most acid solution; pH 7.0 is neutral, and pH 7.6 is alkaline. The concentration of formaldehyde is expressed as

the denominator of the fraction; 10,000 represents a concentration of 1:10,000. Table 3 shows that the reaction progresses slowly, and that in two hours only 5 per cent has been converted in the most acid urine that can be excreted. Assuming a patient to take 4 grams of hexamethylenamin a day and to excrete 1.5 liters of urine containing 75 per cent of the hexamethylenamin, there would be 2 grams per liter or 1:500, and if 5 per cent were converted, the concentration would be 1:10,000. This is in agreement with the figures of Hinman who showed that a patient could excrete free formaldehyde in concentration of 1:10,000.

TABLE 3

The amount of formaldehyde formed from hexamethylenamin 1:600 at varying acidity and at 37°C.

HOURS	pH 4.6	pH 5.0	pH 5.4	pH 6.0	pH 7.0	pH 7.6
1	25,000	27,000	32,000	56,000	Trace	None
2	10,000	12,000	23,000	60,000	Trace	None
3	8,000	11,000	19,000	34,000	Trace	None
4	8,000	11,000	18,000	30,000	100,000	None
24	5,000	6,000	12,000	18,000	55,600	None

pH represents the hydrogen ion concentration of the buffer solution. The concentration of the formaldehyde is represented by the denominator of the fraction, the numerator 1, in every case, being understood. Thus, 5000 equals 1:5000.

After the administration of hexamethylenamin, unless the urine is as acid as pH 6.0, germicidal strength will never be attained in the body, regardless of the time the urine is retained. At pH 5.4, the concentration will be inhibitory after two hours; at pH 5.0, will be inhibitory after one hour; and in three hours, is sufficient to kill 80 per cent of the organisms. At pH 4.6, the concentration after the first hour is sufficient to cause definite antisepsis, and in two hours is sufficient to kill 90 per cent of the organisms.

5. Total amount of formaldehyde formed in twenty-four hour urine standing for twelve hours. Patients received (15 grains) 1 gram of urotropin four times a day, and then the twenty-four-hour urine was collected. Since the determination could not be

made on each separate fresh voided specimen, we preserved the urine with 5 per cent thymol chloroform, and twelve hours later—that is, after the equilibrium had been established—we determined the total hexamethylenamin and the per cent converted. These figures are of course higher than those of freshly voided urine, and are comparable with those of pure hexamethylenamin in solutions of known acidity after twenty-four hours (see table 3). Here too, as table 4 shows, in about fifty cases, we found that the percentage of free formaldehyde was directly proportional to the pH of the urine.

TABLE 4

Relation between acidity of urine and per cent of hexamethylenamin converted into formaldehyde in twenty-four hours

Urine, pH	5.0	5.4	5.8	6.0	6.4	7.6
Formaldehyde, per cent	20	13	8	6	3	0

The per cent of formaldehyde is calculated by determining the hexamethylenamin excreted unchanged and also the free formaldehyde. From this the percentage converted is calculated.

6. *The amount of hexamethylenamin excreted in the urine and the loss of hexamethylenamin in the stomach.* Our figures show that about 60 to 75 per cent of the hexamethylenamin given is excreted in the urine. These figures agree very well with those of Hinman, Hanzlik and Collins, and Falk and Sugiura. It is not safe, however, to assume that this percentage is always present, for although Hinman (1913) stated that kidney disease was without influence, Falk and Sugiura have shown that a damaged kidney will excrete less hexamethylenamin than a normal kidney. Presumably, the loss of hexamethylenamin is due to its partial excretion in the saliva and through the gall bladder, but, as was pointed out by Hinman, the greater part of the loss can be accounted for through conversion into formaldehyde in the acid gastric juice. To test this point, we gave pills coated with salol, which are not dissolved in the stomach, and collected the twenty-four-hour urine. The total excretion, one would expect to be about 10 per cent greater than the average of 60 to 75 per cent. As a matter of fact, it was 10 per cent less,

showing 50 to 60 per cent excretion in twenty-four hours. This shows that although none could have been broken down by the acid gastric juice, the rate of absorption must have been less, because the salol must have been slowly dissolved. This is in agreement with the findings of Hinman. He said that formaldehyde was not increased under these conditions, though he reached the conclusion without making any determinations of the unchanged hexamethylenamin. Hinman (1913) p. 263, says that the use of hexamethylenamin coated with salol did not give a sufficiently marked difference, even in hyperacidity, to recommend it for routine use. "It takes from two to three hours longer for the drug to appear in the urine, and it seems to disappear sooner than when fed in the usual way." The gastric juice acts on the hexamethylenamin, but not more than 25 per cent should be converted, if one follows the suggestion of J. W. Thompson-Walker. He gives the drug with large amounts of water between meals. Probably the best time is one-half to one hour before meals. This leaves the empty stomach rapidly and hence causes less liberation of formaldehyde. If gastric irritation is caused, the salol-coated or keratin-coated pills should be used. They will cause no free formaldehyde in the stomach, but will give slightly smaller amounts excreted by the kidney.

7. *Fluid intake and its effect on the acidity of the urine.* In this clinic, it is the custom to force fluids in all cases showing impaired kidney function. The question arose as to whether such treatment and hexamethylenamin therapy were incompatible. The theory on which the drug had been administered was that the urine must be very small in amount for three reasons: first, to increase the concentration of the drug so that more formaldehyde would be present; second, to increase the acidity; third, to increase the time the urine could be retained in the bladder. The importance is in the order named: first, the urine should always be held for two hours, and better four hours, as the experimental data clearly indicate. Otherwise, insufficient time is allowed for the conversion into formaldehyde, or for the formaldehyde to kill the organisms. Second, we did not anticipate any great changes in the acidity of the urine, because of the

constitution of the urine. The phosphates in the urine are partly acid and partly alkaline, and it is the relative amounts of acid phosphate and alkaline phosphate rather than their actual concentration which determine the pH of the urine. Thus, one can take a mixture of equal parts of acid and alkaline phosphates and dilute it twenty times without any change in acidity. The researches of Henderson and Palmer have shown, however, that the more concentrated urines are the more acid. When more water is given by mouth, more acid producing substance should be given until the proper reaction is reached. Third, the increase in the volume of the urine must be balanced by giving larger doses of hexamethylenamin.

8. *Acidity of the urine.* When giving hexamethylenamin, one should always control the reaction of the urine. How best to produce an acid urine is still an open question. There will be some cases in which the acidity is not so great as one would wish or expect. The most important factors to control are diet and drugs, water intake, exercise, and sleep. Since we have not quantitative data on all these points, we shall not go into an extended discussion of them at present. For a list of acid forming or base forming foods, the reader is referred to the work of Sherman. The water intake has been referred to. In general, the greater the volume, the less the intensity of the acidity. However, it is not proportional to the amount of dilution and is not the determining factor. We have observed that the morning urine is always quite acid, usually the most acid of the day. Exercise is known to increase the acidity of the urine. Of the drugs, the commonest and probably the most satisfactory of those at present used are acid sodium phosphate and benzoic acid or ammonium benzoate. Two gram doses of either can be given four times a day, and should of course be given at a time other than that of administering hexamethylenamin.

In changing the acidity of infected urine, the influence of the organism on the acidity must be taken into account. It has recently been shown by Shohl that when it grows in acid urine, B. coli produces alkali. This is of importance only when the organisms have overcome their period of initial "lag," that is,

in four hours. In infected cases with retention from any cause, it should therefore be more difficult to render the urine acid.

9. Hexamethylenamin from formaldehyde and ammonia. The conditions for the conversion of hexamethylenamin into formaldehyde and ammonia have just been discussed. We were also interested to see whether if free formaldehyde were introduced into an alkaline urine, hexamethylenamin would be formed with consequent loss of germicidal strength. We therefore titrated sterile urine to pH 5.0, 6.0, 7.0, 8.0, and introduced the same number of organisms and the same concentration of formaldehyde, 1:10,000, in each.

TABLE 5

Effect of formaldehyde 1:10,000 added to acid and alkaline urine inoculated with B. coli

CONTROL pH 5.4 NO FORMALDEHYDE		pH 5.0	pH 6.0	pH 7.0	pH 8.0
20 minutes	6,500,000	2,700,000	3,000,000	5,300,000	2,500,000.
1 hour	5,000,000	600,000	690,000	1,500,000	370,000
2 hours	3,000,000	90,000	170,000	200,000	180,000
24 hours	15,000,000	0	0	0	0

The number of living organisms per cubic centimeter are indicated by the figures.

In all solutions to which formaldehyde had been added, the organisms were killed in twenty-four hours. In twenty minutes, 20 to 40 per cent, in one hour 85 to 95 per cent, in two hours 94 to 97 per cent, and in twenty-four hours 100 per cent were killed. This indicates that it is a safe and correct procedure to irrigate a bladder containing either acid or alkaline urine with dilute solutions of formaldehyde, as has been suggested by Burnam. In alkaline urine, the germicidal effect becomes apparent before any slight tendency to form hexamethylenamin. In such treatment, of course, a solution stronger than 1:10,000 would be employed; and Burnam has used solutions of formaldehyde as concentrated as 1:250.

10. Antiseptic and germicidal values of urine. To test more accurately whether the conditions for the transformation and action of urotropin in the body were comparable to our laboratory

tests, we gave hexamethylenamin (grains 15) four times a day to a patient without any infection, and then took a sterile specimen of his urine. To this we added a definite number of B. coli and plated and counted the organisms. The organisms were all killed in two hours as shown in table 6.

TABLE 6

The per cent of B. coli killed when added to the urine of a patient taking hexamethylenamin

	43,000,000	4,000,000	400,000
15 minutes	91	92.5	94
1 hour	93	94.5	96
2 hours	100	100.0	100
24 hours	100	100.0	100

The per cent killed was calculated from number of organisms growing in a control urine without any hexamethylenamin. Urine and control urine pH 5.6.

The urine was in the bladder about four hours—that is, an average of two hours—and the time must be added to that given here.

Thus, after a moderate dose of hexamethylenamin (15 grains four times a day), a patient voided urine which was definitely germicidal to organisms introduced into it in two hours.

DISCUSSION

Our work can perhaps best be summed up by quotations from the excellent article by Hinman (1915), p. 46.

Of all substances, hexamethylenamin is the most efficient in the largest number of cases, but its limitations are so numerous and pronounced as to make its value felt only in selected cases, and it should not be given in the routine way that is at present almost universally practised. It depends for its action on conversion in an acid urine into formaldehyde. Urinary acidity and the reaction time of the conversion are the two most important factors.

Page 48: The simple chemical change from hexamethylenamin into formaldehyde is slow and gradual, and it is seen, even with a uniform excretion, the longer the drug is allowed to accumulate in the bladder,

the greater becomes its concentration and the more complete its conversion. This necessary time factor completely nullifies the value of the drug as an internal urinary antiseptic in many urinary conditions. Polyuria and frequent urination prevent this accumulation, and the constant outflow from the kidney, except in hydronephrotic cases, accounts for the fact that the drug is of little if any value at the level of the kidney. The same reason explains the poor results in cases with a retention catheter and in all cases with urinary fistulas. In postoperative prostatics, who particularly need an efficient urinary antiseptic, hexamethylenamin is practically valueless until continence returns. It is valueless for urethral antisepsis, no matter what the infection.

The value of hexamethylenamin is greatest as a bladder prophylactic before and following instrumentation, when the above mentioned urinary conditions are not present, and inasmuch as formaldehyde is equally bacteriostatic toward all organisms, the usefulness of the drug in this group of cases will probably never be supplanted.

The results of our experiments show definitely that the amount of formaldehyde liberated from hexamethylenamin is dependent upon the acidity of the urine. For each hydrogen ion concentration, a definite amount can be expected in a definite time. Therefore, we feel that in treating a patient with hexamethylenamin, satisfactory results cannot be accomplished unless the pH of the urine is determined and the amount of formaldehyde measured on fresh specimens. Acid should be given, proper diet instituted, water restricted, urotropin given in 15-grain doses with water between meals, and the urine should have a formaldehyde content of 1:10,000 or greater, and a reaction of pH 5.4 or greater. No one of these factors alone will be successful, but if combined we can secure better results in treatment than have heretofore been obtained. By the methods which have been given and are practical for clinical use, treatment can be placed on a definite basis. It is only necessary to determine accurately the amount of formaldehyde present and the hydrogen ion concentration of the urine.

SUMMARY

1. Formaldehyde solutions of 1:5000 to 1:10,000, in two hours, at body temperature, will kill 80 to 90 per cent of B. coli.

2. The rate of transformation and the amount of formaldehyde formed from hexamethylenamin depend on the hydrogen ion concentration of the urine.

3. The urine must be as acid as pH 5.4 to obtain 80 to 90 per cent antisepsis in two hours.

REFERENCES

(1) Burnam, C. F.: An experimental investigation of the values of hexamethylenamin and allied compounds. Archiv. Int. Med., Chi., 1912, x, 324–334.

(2) Chick, H.: Investigation of the laws of disinfection. Jour. Hyg., Lond., 1908, viii, 92–158; 654–697.

(3) Churchman, J. W.: The treatment of bacteruria by internal medication, a clinical and bacteriological study. Johns Hop. Hosp. Reports, Balt., 1906, xiii, 189–206.

(4) Clark, W. M., and Lubs, H. A.: The colorimetric determination of hydrogen ion concentration and its application to bacteriology. Jour. Bact., Balt., 1917, ii, 1–35, 109–136, 191–236.

(5) Collins, R. J., and Hanzlik, P. J.: The colorimetric method for the estimation of free formaldehyde and hexamethylenamin. Jour. Biol. Chem., Balt., 1916, xxv, 231–238.

(6) Davis, E. G.: Urinary antisepsis. A study of the antiseptic properties and the renal excretion of compounds related to phenolsulphonphthalein: preliminary report. Jour. Am. Med. Ass., Chi., 1918, lxx, 581–585.

(7) Davis, D. M., and Swartz, E. O.: The testing of germicidal substances against the gonococcus. Jour. Inf. Dis., Chi., 1920. To appear.

(8) Dunning, H. A. B.: Detection and quantitative estimation of minute quantities of formaldehyde in presence of hexamethylenamin and methyl alcohol in presence of ethyl alcohol. Am. J. Pharm., Phil., 1913, lxxxv, 453–459.

(9) L'Esperance, O. R. T., and Cabot, H.: The excretion of formaldehyde by the kidneys of patients taking hexamethylenamin. A study of Burnam's test. Bost. Med. and Surg. Jour., Bost., 1912, clxvii, 577.

(10) Erulkar, A. S.: Hexamine, its use and misuse. Practitioner, Lond., 1916, xcvi, 405–408.

(11) Falk, K. G., and Sugiura, K.: The elimination of hexamethylenetetramin as an index of renal function. Jour. Pharm. and Exper. Therap., Balt., 1917, ix, 241–245.

(12) Hanzlik, P. J.: The liberation of formaldehyd and decomposition of anhydromethylenecitric acid and its excretion in urine, with comments on "Citarin" and "Helmitol." Jour. Urol., Balt., 1920, iv, 143–165.

(13 Hanzlik, P. J., and Collins, R. J.: Hexamethylenamin: The liberation of formaldehyde and the antiseptic efficiency under different chemical and biological conditions. Archiv. Int. Med., Chi., 1913, xii, 578–612.
(14) Henderson, L. J. and Palmer, W. W.: On the intensity of urinary acidity in normal and pathological conditions. J. Biol. Chem., Balt., 1913, xiii, 393–405.
(15) Henderson, L. J., and Palmer, W. W.: On the extremes of variation of the concentration of ionized hydrogen in human urine. Jour. Biol. Chem., Balt., 1913, xiv, 81–85.
(16) Henderson, L. J., and Palmer, W. W.: On several factors of acid excretion. Jour. Biol. Chem., Balt., xvii, 305–315.
(17) Hinman, F.: An experimental study of the antiseptic value of the internal use of hexamethylenamin with the report of a simple clinical method of quantitative estimation. Tr. Am. Assn. Genito-Urin. Surg., N. Y., 1913, viii, 235–268.
(18) Hinman, F.: Urinary antisepsis: a clinical and bacteriological study. Tr. Sec. on Genito-Urin. Fis., Am. Med., Chi., 1915, lxv, 36–59.
(19) Höst, H. F.: Über Reaktionsbestimmungen des Harns. Ztschr. Klin. Med. Berl., 1915, lxxxi, 266–271.
(20) Höst, H. F.: Über Urotropinals Desinfiziens der Harnwege. Ztschr. Klin. Med., Berl., 1915. lxxxi, 272–284.
(21) Jenness, B. F.: Burnam's test for formaldehyde in the urine. Jour. Am. Med. Assn., Chi., 1913, lx, 662.
(22) Jorrison: Method for formaldehyde. Bull. Soc. Chem. Belg. 1897, xi, 211. Cited by Nicolaier.
(23) Jordan, A.: Action of urinary antiseptics. Biochem. Jour., Lond., 1911, v, 279.
(24) Levy, L. H., and Strauss, A.: A clinical and bacteriological study of hexamethylenamin as a urinary antiseptic. Archiv. Int. Med., Chi., 1914, xiv, 730–742.
(25) Nicolaier, A.: Über die Therapeutische Vervendung des Hexamethylentetramin. Cent. f. med. Wissen. 1894, no. 51. This is the discoverer of the therapeutic use.
(26) Nicolaier, A.: Expermentelles und Klinisches über Urotropin, Ztschr. f. Klin. Med., Berl., 1899, xxxviii, 350–416. This article reviews his work and gives 85 references.
(27) Rimini: Ann. Farmacol. 1897, xvii, 97. Cited by Hinman.
(28) Shohl, A. T.: Determination and significance of acidity. Bull. Johns Hopkins Hosp., Balt., 1920, xxxi, 152–158.
(29) Shohl, A. T.: Changes in acidity or alkalinity of the urine produced by B. coli as measured by the final hydrogen ion concentration. Jour. Urol., Balt., 1920, iv, no. 4.
(30) Shohl, A. T., and Janney, J. H.: The growth of Bacillus coli in urine at varying hydrogen ion concentrations. Jour. Urol., Balt., 1917, i, 211–229.
(31) Sherman, H. C.: Chemistry of food and nutrition. 8. New York, 1918, 454 pp.

(32) Smith, G. G.: Excretion of formalin in urine. An inquiry into the accuracy of Burnam's test. Bost. Med. and Surg. Jour. Bost., 1913, clxviii, 713–716.

(33) Sollman, T.: Formaldehyd derivatives. Their fate in the body together with observations on some other urinary antiseptics. Jour. Am. Med. Assn., Chi., 1908, li, 818–824.

(34) Talbot, F., and Sisson, W. R.: Some factors which influence the excretion of formalin in children and infants taking hexamethylenamin (urotropin). Bost. Med. and Surg. Jour., Bost., 1913, clxviii, 485–494.

(35) Walker, J. W. T.: Urinary antiseptics. Brit. Med. J., Lond., 1913, ii, 654–660.

(36) Walker, J. W. T.: Hexamine as a urinary antiseptic. Med. Press and Cir., Lond., 1916, clii, 304–308.

(37) Wiseman, J. R.: Albuminuria and hematuria following the administration of hexamethylenamin. Am. Jour. Med. Sci., Phil., 1917, cliv, 264–279.

TUMORS PRIMARY IN THE URETER[1]

WM. C. QUINBY

Boston

Neoplasms arising in the ureter are not at all frequent. In their review of 1903, Albarran and Imbert were able to collect only thirteen such cases, and since this date, there have appeared in the literature only about the same number.

Such tumors are either ectodermal or mesodermal in origin, the former variety predominating markedly in number. Jeanbrau, writing in the Encyclopedie Française d'Urologie[2] in 1914, reports thirty instances of such tumors. He found that in the epithelial group there were seven papillomata, two papillary adenomata, three papillary epitheliomata, and fourteen non-papillary epitheliomata. In the group of mesodermal tumors there were but four cases. Of these, three were one form or another of sarcoma, while the fourth was a fibro-lipoma.

The following case is therefore of considerable interest:

The patient was a single woman of forty, a school teacher, who entered the Peter Bent Brigham Hospital on November 24, 1919. Throughout her life she had had no illness of consequence. She dated her present illness from November 7, 1919, when, after a slightly unusual exertion she noticed a dull aching pain in the left side. This pain had been somewhat intermittent since, and had never been severe. There had been no nausea, no vomiting, and no fever. There had been no association of this pain with the bladder, and the urine as far as the patient knows, was entirely normal.

Physical examination showed a very healthy appearing, middle-aged woman with no abnormality except that in the left side of the abdomen, below and outside the umbilicus, there was found a smooth, oval, firm mass, not moving with respiration, not tender, but which

[1] Read before the American Association of Genito-Urinary Surgeons, Rochester, Minnesota, Tuesday, June 1, 1920.

[2] Encyclopedie Française d'Urologie, Vol. III, 1914, pp. 917–926.

could be pushed about the abdominal cavity for a short distance with ease. Gastro-intestinal studies by x-ray, after the ingestion of barium, gave no abnormal findings. The examination of the urine and of the blood were both normal.

Fig. 1. Ureterogram Showing Catheter Arrested at About Crest of Ilium and Imperfectly Filled Ureter and Kidney Pelvis above Area of Obstruction

On cystoscopic examination the bladder was normal and there was apparently a normal efflux of urine from each ureter. On the right side the ureteral catheter passed for the usual distance without obstruc-

tion. On the left side, however, the catheter stopped at 14 cm. and from this side the flow of urine was very slow. Pyelogram, after injection, showed the left kidney in its normal position, and below this a definite distortion and obstruction in the ureter which was curved upward, slightly dilated, and the shadow ended in an abrupt tip. This point lay opposite the iliac crest. The kidney was slightly enlarged and the ureter was somewhat dilated above the obstruction. There was no evidence whatever of infection in the urinary tract.

From the appearance of the x-ray plate it would seem that only two conditions could cause the findings: first, an involvement of the ureter by some extra-ureteral infection such as a broken down retro-peritoneal gland; or, second, more probably, definite involvement of the ureter by neoplasm. Palpation of the mass in the flank showed it to be entirely distinct from the kidney.

Under a pre-operative diagnosis of neoplasm involving the left ureter, operation was undertaken on December 10, 1919, by the resident surgeon, Dr. E. C. Cutler. The peritoneal cavity was entered through the left rectus muscle, the intestines being retracted toward the middle line. A definite tumor mass was at once exposed lying beneath the peritoneum just to the left and below the bifurcation of the aorta into the common iliac arteries. Immediately over the upper pole of this small tumor mass, which was as large as a baby's fist, and quite firmly attached, ran the mesentery of the large bowel containing the inferior mesenteric artery, and immediately to the right of the mass, overlying a portion of it, lay the iliac vein. The tumor was intimately adherent with the peritoneum. Immediately overlying its anterior surface, and in the peritoneum itself, was an elaborate meshwork of fine vessels. Search on either side did not reveal the ureter, and it was decided to attempt enucleation, searching for the ureter as the definition of the tumor mass progressed. The peritoneum was therefore incised in an elliptical fashion at either border of the tumor, all the fine vessels being clamped and tied off. Having thus freed it from the peritoneum by blunt dissection it was possible to free the mass from the surrounding structures, especially posteriorly, where it was very definitely adherent, although apparently it lay within a definite capsule of its own. This fixity seemed to be due to the fact that it lay in the very center of a multitude of fine nerves, quite as though it lay in the center of a plexus of a sympathetic system. It was necessary to divide innumerable small fibers during the progress of the operation. Without, however, breaking into the tumor we were able

finally to free it definitely on both sides and beneath without any very large vessel having to be cut. At this stage the ureter was encountered at both lower and upper ends of the tumor mass, through which this structure passed. It was now attempted to dissect the ureter free from the tumor mass, but after practically completing this it was seen

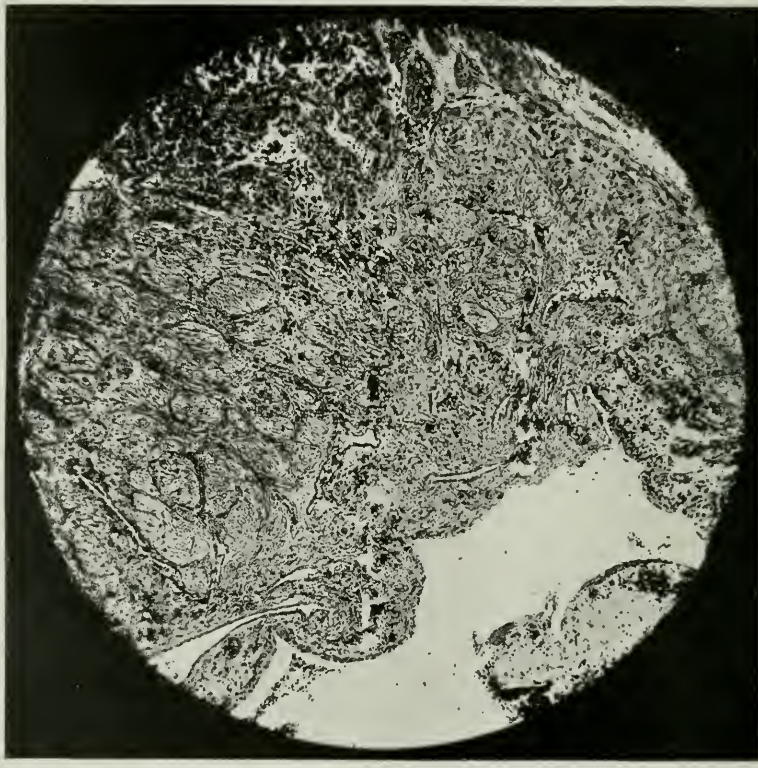


Fig. 2. Lumen of Ureter Showing Tumor in Upper Left Hand Corner, Also in Lower Center. Low Power

that the tumor grew into or from the ureter, so that it became evident that this would leave so much of the lesion behind that it was thought most unwise to continue. The ureter was therefore dissected downwards towards the bladder as far as possible and cut across. Dissection was then carried upwards towards the kidney end of the ureter, and when the normal ureter was encountered it was cut across.

Pathological examination of the tumor showing it to be probably malignant and also possibly of renal origin, a nephrectomy was done ten days later. The kidney was found to be entirely normal.

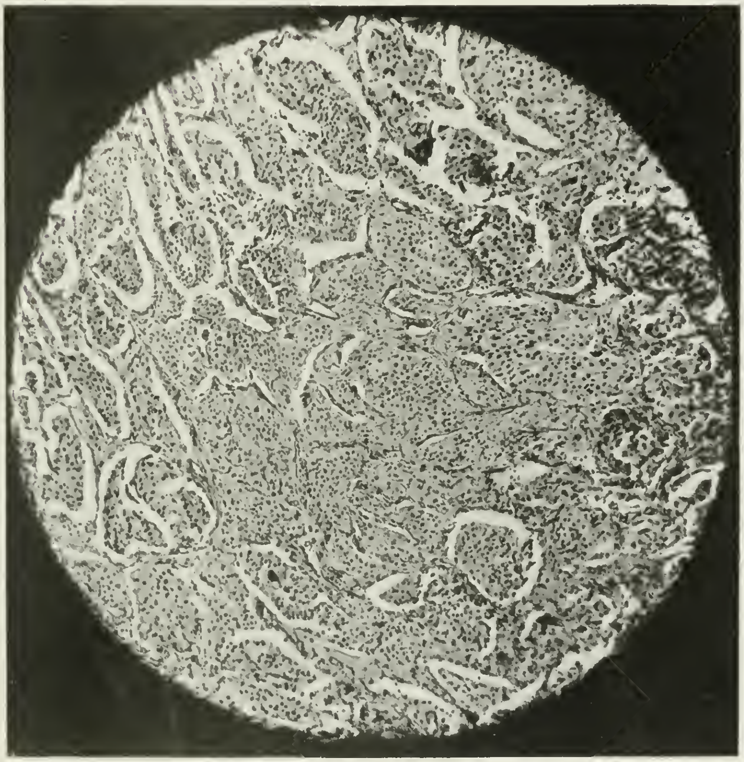


Fig. 3. Center of Tumor Mass. Note Nodular Arrangement of Cells. Low Power

On January 4, 1920, the patient was discharged from the hospital in excellent general condition, and examination made a week ago showed no evidence whatever of recurrence, the patient being in excellent health.

The pathological report of this tumor was made by Dr. S. B. Wolbach, and is as follows:

Gross description. The specimen consists of an ovoid tumor mass weighing 21 grams and measuring 6 by 5 by 1 cm. The outer surface is of cherry red color and shows it to consist of nodules all about 1 cm. in diameter, raised and having a somewhat firmer consistence than the remainder of the tissue. At one pole there is attached to the mass a portion of ureter measuring about 3 cm. in length which runs along the outer surface of the mass, and the lumen of which at one point is completely obliterated by tumor tissue. The consistence of the tumor

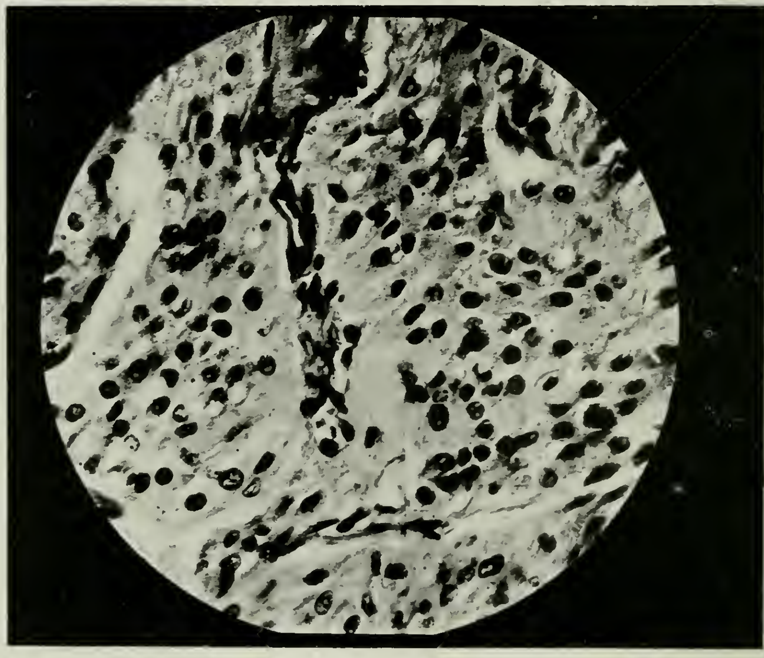


Fig. 4. High Power Showing Septum with Capillary Lined by Endothelium

is that of normal liver, but throughout its substance there may be felt firmer, fairly circumscribed nodules.

Cut section shows a surface quite irregularly mottled with various degrees of red color. Toward the surface there are areas quite similar in color and appearance to kidney cortex. Throughout the remainder of the section the color varies from cherry to dark red, considerable hemorrhage apparently having taken place. Encircling the tumor mass is a well defined, pinkish, fibrous appearing capsule measuring

0.5 to 1 mm. in thickness, which at a few points sends off fibrous strands into the substance of the mass.

Microscopic examination. Sections through the main tumor show a fairly uniformly constructed growth composed of columns of cells several deep, separated by a delicate connective tissue stroma which is nearly everywhere penetrated by capillaries. This alone is a striking feature of the tumor, in that the supporting tissue in most places consists of two layers of connective tissue containing an endothelial lined growth. In a few portions of the tumor these spaces are greatly distended with blood. Here and there throughout the tumor are heavier supports composed of connective tissue and smooth muscle bundles. The epithelial cells of the tumor are closely packed. They are irregularly polyhedral in shape except where they have become separated owing to necrosis, and there they assume a round shape. The cells are fairly large, roughly the size of renal epithelium. Even when closely packed together individual cells are often separated by a cuticular-like border. Another feature of the cells is that most of them contain small vacuoles in which may be found, with phosphotungstic acid hematoxylin stain, minute curved rods and granules, the latter often paired. It is probable that these rods and granules are fibrin derivatives. In a few places cells show a tendency to tubular arrangement. The suggestion of a possible renal origin is striking. There are no fibrils or cytoplasmic processes in connection with the tumor cells. The presence of a cuticular border occurs on a few occasions in all parts of the tumor. Mitotic figures are extremely rare.

DISCUSSION

The tumor is unquestionably an invading tumor, but probably one not liable to metastasis. It is definitely an invading tumor and therefore must be considered malignant. Its structure is definitely edematous and of a unique type. It may properly be called a mesothelioma. The pale appearance of the tumor and its location are compatible with renal anlage origin. There is nothing about it to suggest a neuroblastoma or an adrenal tumor.

Diagnosis. Mesothelioma, probably of renal anlage origin.

447.

THE LATER DEVELOPMENT OF THE URETHRA IN THE MALE

FRANKLIN P. JOHNSON

From the Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

INTRODUCTION

The early development of the urogenital structures in man has been thoroughly studied, and its essential features are now quite generally understood by all embryologists. Among the most noteworthy investigations on this problem are those of Born (1), Keibel (13) and Pohlman (22), followed more recently by the work of Felix (8). The later development, however, especially the transformations which take place in the late fetal stages, has been less well worked out. Mention, however, should be made of the creditable investigations of Pallin (19), Lichtenberg (16), Lowsley (17), Paschis (20), and Eggerth (6). My own investigation was undertaken for the purpose of studying the development of the smaller urethral glands, their number and distribution, and the formation and constancy of the mucosal folds of the urethra. To this has been added a number of observations on the development of the prostate, Cowper's glands, the prepuce and other closely related structures of the urethra.

The method employed has been that of serial sections, the whole pelves of the younger stages being cut serially. For the older stages, the urethra with its adnexa were dissected out, but into a number of segments, then embedded in paraffin and cut in sections of 15 to 30 micra, special care being taken to preserve the order of the whole series. In sectioning the late fetal, newborn and postnatal stages, only portions of the segments were cut, the remainder of the segments being preserved and subsequently cut if it was deemed necessary. From the series of sections thus made, wax reconstructions after the Born method were made of

certain of the more important stages. The graphic method of reconstruction was also employed in certain instances.

The investigation was undertaken under the supervision of Professor Hugh H. Young of the Brady Urological Institute of the Johns Hopkins Hospital, and continued in the Department of Anatomy of the University of Missouri. The work was completed in the Department of Surgery of the Yale Medical School. Acknowledgment is made to Professor Streeter of the Carnegie Embryological Institute for the use of materials and for much valuable aid; and to both Professors Young and Streeter for many valuable criticisms and suggestions. To Mr. Wm. Ditusch grateful acknowledgment is also made for the painstaking and accurate drawings of the wax models.

Inasmuch as the earliest stage included in my study is an embryo of 55 mm. crown-rump length, it is necessary, in order to properly take up the later development to review briefly the embryology of the urethra up to this stage. The following summary, taken largely from the work of Felix (8), is an attempt to tabulate only the important steps in the formation of the urethra and other structures with which it is closely related.

As is well known, the urethra in man is a derivative of the entoderm, being derived from a cut-off portion of the primitive hind-gut. The first step in its development consists in the formation of the cloaca. This is formed in the first weeks of embryonal life when the posterior end of the hind-gut comes in contact and fuses with the ectoderm of the lower part of the ventral body wall. The plate of epithelium formed by this fusion, comprised of an inner layer of entoderm and an outer layer of ectoderm, constitutes the cloacal membrane, which occludes the openings of the cloaca and its later derivatives for a considerable period of time. Extending orally from the ventral wall of the cloaca is the slender allantoic duct, which passes out into the umbilical cord. In embryos of from 5 to 6 mm. in length, the cloaca undergoes a longitudinal splitting in the frontal plane. This takes place by a downward growth of the uro-rectal septum. When the growth of this structure is complete, the dorsal portion or rectum is entirely separate from the remaining ventral portion of the cloaca.

In the meantime, the primary excretory ducts, later becoming the Wolffian ducts, have reached and fused with the ventral portion of the cloaca. A second division now takes place, incompletely dividing the ventral portion of the cloaca into an upper portion which represents the bladder and urethra and a lower portion, the urogenital sinus.

While the above changes are taking place, the genital tubercle arises from the anterior body wall just above the urogenital membrane. With the further development of the genital tubercle or phallus, the urogenital sinus is drawn out with it, so that the urogenital membrane comes to lie on its rectal surface. Two parts of the urogenital sinus are now to be recognized, a phallic portion which is situated within the genital tubercle, and a pelvic portion, situated within the body of the embryo.

The Müllerian ducts, arising in conjunction with the genital glands, extend from above downward between the Wolffian ducts and reach the posterior surface of the pars pelvina of the urogenital sinus. In embryos of from 22 to 28.5 mm. in length, these ducts fuse together in their lowermost portions to form an unpaired median tube, the so-called utero-vaginal canal.

The Wolffian ducts in the male remain as the vasa deferentia; in the female they degenerate, small portions remaining to form Gärtner's canal and a portion of the epoophoron. The utero-vaginal canal in the female gives rise to the uterus and vagina, the un-united portions of the Müllerian ducts forming the Fallopian tubes. In the male the uterovaginal canal largely degenerates, the lowermost portion only remaining to form the vagina masculinus.

It is important at this point to call attention to certain confusing terms; namely, ventral and dorsal, and anterior and posterior, as applied to the walls of the urethral tube. The confusion results from the S-shaped curvature which the male urethra assumes during embryonic life. In the prostatic portion of the urethra, the terms dorsal and ventral, or posterior and anterior are definitely clear. Thus no ambiguity exists in speaking of the anterior and posterior, or ventral and dorsal lobes of the prostate. However, if one starts on the ventral wall of the prostatic portion and fol-

lows it down into the proximal half of the cavernous urethra, it becomes directed cephalad. Followed further into the distal half of the cavernous (penile) portion it comes to lie nearer to the socalled "dorsum" of the penis, i.e., toward the dorsal vein. Similarly the dorsal wall of the prostatic urethra becomes the ventral wall in the penis. The terms "anterior" and "posterior" are scarcely more suitable when all portions of the urethra are taken into consideration. The terms "roof" and "floor" are much less confusing but they do not permit the formation of appropriate adjectives. After careful consideration of this matter, I have decided to employ the terms "pubic" and "rectal" to denote the surfaces of the urethra, meaning by the former that surface which lies nearer to the pubis, i.e., the ventral wall of the prostatic urethra, the roof of the cavernous portion, and that wall which lies nearer to the dorsal vein in the dependent portion of the penis; by the rectal surface, that which lies nearer the rectum.

OBSERVATIONS

Embryo no. 224, 55 mm. crown-rump length. Length of urethra 6 mm. A mid-sagittal section of the pelvis of this embryo is shown in figure 1. The true urethra, i.e., that portion corresponding to the whole of the urethra in the female, begins at the base of the bladder and extends to the urogenital sinus. The line of demarcation between the base of the bladder and the urethra is seen as a slight constriction on the dorsal wall of the tube. Although the dorso-ventral diameter of the bladder is no greater than that of the urethra, the lateral diameter is considerably greater, so that from a study of the serial sections the vesico-urethral junction is more clearly apparent. The distal end of the urethra proper, although directly continuous without change of caliber or structure with the urogenital sinus, terminates at the point where the utero-vaginal canal joins the sinus. The true urethra is short and relatively broad and is directed caudally and somewhat dorsally between the symphysis pubis and the rectum. Just before it terminates, it presents a well-marked dorsal protuberance which marks the upper limit of the cristae

urethralis and below which the urethra bends ventrally. The epithelium of the true urethra is not essentially different from that of the bladder, being composed of from four to five layers of cells, the innermost of which are distinctly columnar and have their nuclei situated toward the surface ends of the cells. It is separated from the surrounding mesenchyme by a distinct basement membrane.

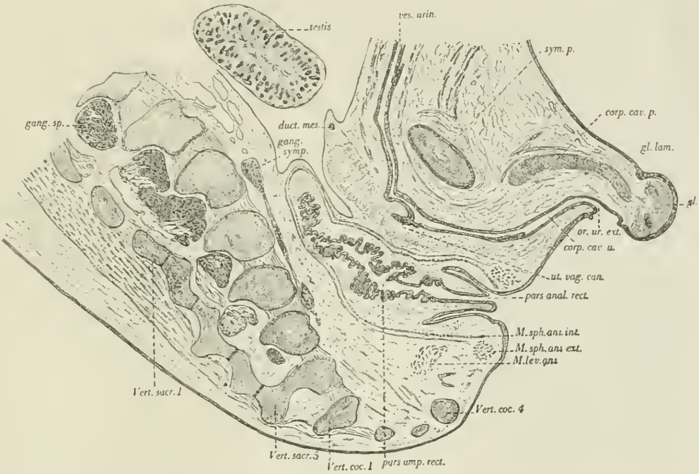


Fig. 1. Embryo No. 224, 55 mm. Long

Mid-sagittal section (composite of sections 56 to 58). × 8

The epithelium of the urethra is thrown into a number of longitudinal folds of which the ventral four or five are shallow and not well-marked. On the dorsal wall of the lower one-fourth of the urethra is a deep fold, the cristae urethralis, through which the Wolffian ducts and utero-vaginal canal reach the urethra.

The urogenital sinus, commonly considered as a part of the urethra in the male, is directly continuous with the true urethra and reaches the exterior on the rectal surface of the phallus at about its middle. It presents two definite curvatures, a ventral bend in the pars pelvina and a dorsal one on the pars phallica. The pars pelvina lies between the symphysis pubis and the lower part of the rectum. The pars phallica lies within the

proximal half of the phallus near its rectal surface. Its lumen is patent throughout, its epithelium composed of only two to four layers of cells. The epithelial tube is somewhat flattened dorsoventrally in the pelvic portion and is without folds; that of the phallic portion presents single longitudinal folds on its rectal and lateral walls.

Of the glands of the urethra, the prostate, the bulbo-urethral (Cowper's) and the small sinus glands (Littre's) have all made their appearance at this stage. The prostate is represented by a number of solid bud-like projections of the urethral and sinus epithelium. Of these there are seven on each side laterally, four pairs posteriorly above the junction of the urethra and utero-vaginal canal and two pairs on the pubic surface, making a total of twenty-six gland buds in all. Some of these prostatic glands are definitely formed epithelial outgrowths; others are merely slight thickenings of the epithelium. None is provided with a lumen. Lowsley (17) has reported the absence of prostatic glands in an embryo of 50 mm., while in his next stage, an embryo of 75 mm., sixty-three tubules were present.

The bulbo-urethral glands are represented by two cylindrical epithelial outgrowths. They arise side by side on the rectal surface of the distal portion of the pars pelvina and are directed bladderward, lying in close relation to the urogenital sinus. They are solid except where they join the epithelium of the sinus.

The small sinus glands are represented in my 55-mm. specimen by only two small epithelial buds. They are located in the midline on the pubic wall of the pars phallica and are smaller than the epithelial buds of the prostatic glands.

The genital tubercle or penis is covered by a stratified epithelium varying in thickness from five to eight layers of cells and being thickest over the glans. The glans, which comprises almost one-half of the length of the whole penis is already definitely marked off from the shaft of the penis by a constriction on its dorsal and lateral walls. At this constriction the epithelium is thicker and presents a transverse semicircular projection or lamella into the mesenchyma of the penis (fig. 1). This projection, called by Fleischmann (9) the "glandar lamella," definitely

marks off the glans penis and is destined to play an important rôle in the formation of the prepuce.

Within the penis the two corpora cavernosa penis are plainly visible. They are cylindrical bodies extending from the rami ischii as far as the glans. They are composed of densely packed differentiating mesenchymal cells, but contain as yet no blood sinuses.

Embryo no. 195, 65 mm. Length of urethra, 8.5 mm. The urethra of this embryo is shown in figures 13 and 14. The true urethra and urogenital sinus extend as a continuous tube from the neck of the bladder to the phallus and presents its characteristic S-shaped curvature. Opening into its proximal portion, a short distance below the neck of the bladder are the two Wolffian ducts with the utero-vaginal canal between them, the point of entry of which divides the male urethra into its two primary divisions. The urethra may be further divided at this stage into prostatic, membranous, and cavernous portions, thus following the generally accepted anatomical nomenclature. Although this method of division of the urethra is without embryological justification, its usage has become firmly established in gross anatomy and from this stage henceforward it is employed in the present paper.

The prostatic urethra includes the whole of the true urethra and the proximal one-third of the urogenital sinus. Beginning at the base of the bladder and extending to the membranous urethra, it lies between the symphysis pubis and the upper part of the rectum. It is directed caudally to the point where it is joined by the utero-vaginal canal and then turns sharply ventrally. Its epithelial tube, which is patent throughout, is widest in the region where it is joined by the ejaculatory ducts. It presents several shallow irregular folds on its pubic and lateral surfaces, and one deep and broad fold on its rectal surface. The latter fold, the crista urethralis or verumontanum is pierced by the Wolffian ducts and the utero-vaginal canal, as shown in figure 13. The seminal vesicles are seen in the model as lateral swellings of the Wolffian ducts, as has been described by Watson (25).

Numerous gland buds are to be seen extending everywhere from the prostatic portion of the urethra. These are, as is well-known, the beginnings of the prostatic glands. They arise from the pubic, rectal and lateral walls of the urethra, not only below the openings of the genital ducts, but above them for a short distance as well. Following Lowsley's description (17), the prostatic tubules arise from five different foci, as follows: (1) from the floor (rectal surface) of the urethra above the openings of the Wolffian ducts constituting the middle lobe of the adult prostate. Four gland buds, two on each side are seen in this position in my model. (2) From the floor of the urethra below the openings of the Wolffian ducts, forming the posterior lobe. In my model there are ten glands present in this position. (3) and (4) From the right and left lateral walls of the urethra, constituting the right and left lateral lobes, and which are represented in my specimen by nine and ten glands, respectively. (5) From the anterior wall, forming the anterior lobe; four or five small knob-like elevations in my specimen. Of all these tubules, about thirty-eight in number, those of the posterior and lateral walls are the largest.

The membranous urethra is that portion which is surrounded by the M. sphincter urethrae membranaceae. The fibers of this muscle are already differentiating and the muscle appears as an incomplete band about the urethra, but not clearly marked off from the musculature of the prostate. The membranous urethra is smaller in diameter than the prostatic urethra, is flattened dorso-ventrally, and presents but a single fold. This is located on the rectal wall and is the direct continuation of the verumontanum. The membranous urethra is entirely devoid of glands.

The proximal one-half of the cavernous urethra is more rounded and shows several irregular folds. On its rectal surface are seen the bulbo-urethral or Cowper's glands. They are directed bladderward, coursing parallel to and almost in apposition with the urethral epithelium. The urethral bulb, within which they lie, is just beginning to show itself. Lichtenberg (16) was unable to make out the outlines of the bulb in a 60-mm. embryo. The

ducts of the bulbo-urethral glands are for the most part solid cords of epithelium, but here and there along the ducts, small, centrally-placed cavities, entirely discontinuous with one another, are found which represent the beginnings of the lumens. Although Lichtenberg describes the bulbo-urethral glands as strongly branched in an embryo of 68 mm., there is no evidence of a branching in my 65 mm. specimen.

The distal half of the cavernous urethra lies for the most part within the penis and terminates on the rectal surface of the glans. It presents a sweeping curvature, the concavity of which is on the rectal surface. Its lumen is narrow and is encroached upon by several very definite longitudinal folds of the mucous membrane. Of these there are three, right and left lateral and a rectal fold. Eggerth (6) shows similar folds in his model of a 30-mm. embryo, but he regards as folds, however, not the invaginations of the mucosa into the lumen of the urethra, but the furrows in between them. In other words, he has viewed the epithelium from the outside and applies the term "fold" to the ridges of epithelium which course longitudinally on the outside of the urethral tube. This point of view, however, is confusing, inasmuch as what are usually regarded as folds are those elevations of the mucosa which one sees upon opening the lumen of a hollow viscus.

The small sinus or urethral glands are the only glands of this portion of the urethra. They appear as small knob-like outgrowths from the dorsal epithelial furrow of the urethra. As seen in the model in figure 15 eight such projections are present, the anterior one of which is the longest. All are solid at this stage.

The penis of my 65-mm. specimen is relatively short and broad. The glans, which makes up about one-half of the whole organ, is clearly marked off from the shaft by the well-developed glandar lamella. This is a solid shelf of epithelium which extends transversely along the inner surface of the epithelium of the penis except on its rectal wall. The external urinary orifice is a longitudinal slit-like opening on the rectal surface of the glans. Above it the dorsal furrow of the urethra is continued forward to the tip of the glans as a solid vertically-placed lamella of epithe-

lium. It has received the name of "urethral plate," Felix (8), figure 15.

The corpora cavernosa penis are well developed mesenchymal cords and contain numerous endothelial strands which are apparently without lumens. The corpus cavernosum urethrae has also made its appearance. It is less dense but contains a greater number of blood vessels than the corpora cavernosa penis. Its proximal end is continued into the bulb of the urethra, the outlines of which, as stated above, are barely visible. Above the bulb, the membranous and prostatic urethrae are surrounded by a vascular tissue not unlike that of the corpus cavernosum urethrae, which is also directly continuous with the latter structures.

Embryo no. 311, 75 mm. Length of urethra, 8.6 mm. (fig. 2). In a male embryo of 75 mm., the urethra, while presenting the same general features as in the 65-mm. stage, presents a more advanced condition, especially as concerns the glands. The prostatic portion shows similar infoldings of its epithelium, there being one large rectal fold, the verumontanum, two small lateral folds, and two or three quite shallow and irregular folds on the pubic surface. While no attempt has been made to count the number of prostatic tubules, it is evident that they are more numerous than in the above-described stage. The longest prostatic tubules again are placed laterally and posteriorly, and many of them are already provided with definite lumens. The two Wolffian or ejaculatory ducts, and the intermediate utero-vaginal canal join the urethra through the verumontanum, tapering down and becoming extremely small in caliber as they unite with the urethral epithelium. The utero-vaginal canal loses its lumen in its lowermost part.

In the membranous urethra, the mucosal folds are shallower, and in the region of Cowper's glands (bulbous urethra), all, with the exception of the fold on the rectal surface, are absent. Cowper's glands are represented by bilaterally placed, elongated ducts, related to the urethra in a manner similar to that of the previously-described stage. The ducts lie close to the median raphe which divides the bulb into right and left halves. Both ducts are of equal diameter (0.059 mm.) and show definite lumens except in

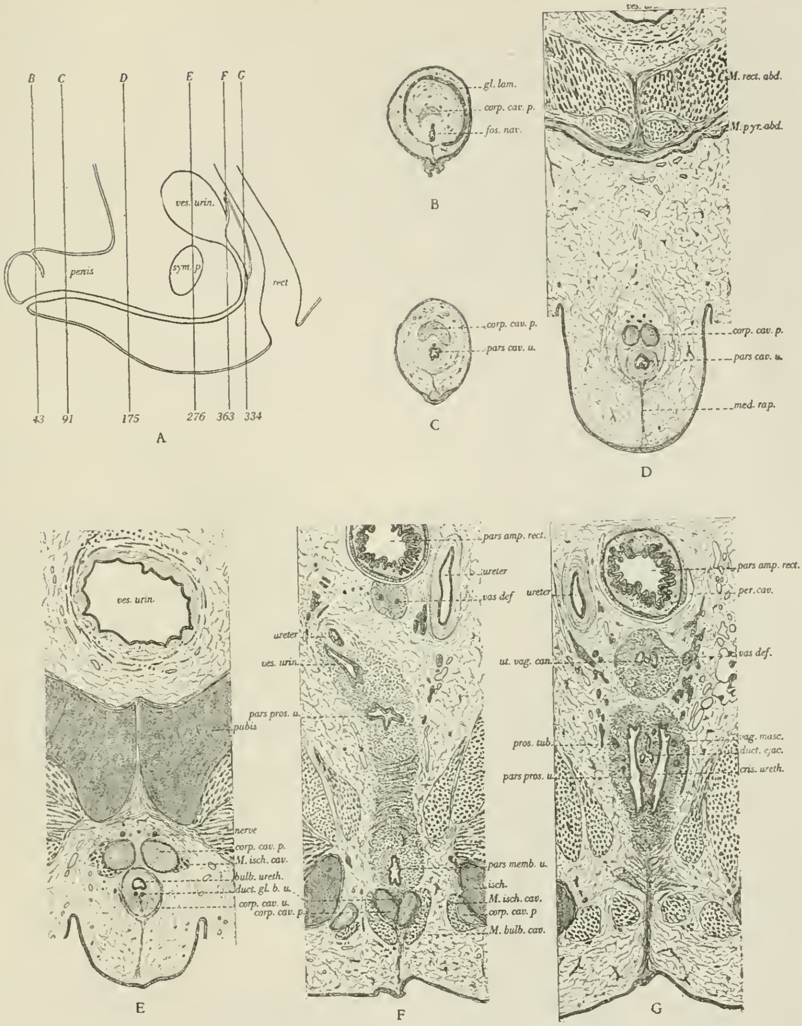


Fig. 2. Embryo No. 311, 75 mm. Long

Frontal sections through the pelvis. *A* is a key-figure showing the levels at which the sections *B* to *G* have been taken. × 8.5.

their deeper portions. The right which shows no terminal branching, is 1.46 mm. in length, and its blind end, although reaching the posterior limit of the bulb, is entirely intra-bulbar. The left gland is somewhat more advanced in development, being 1.7 mm. in length. It is provided with four or five lumenless branches, which pierce the bulb of the urethra posteriorly and are therefore extra-bulbar in position. Inequalities in the development of Cowper's glands have been shown by Eggerth (6) to be the rule rather than the exception. Accessory bulbo-urethral glands, such as have been described by Lichtenberg (16) in embryos of 70 and 210 mm. in length, are absent in this specimen.

The remainder of the proximal half of the cavernous urethra is devoid of folds except for the downward continuation of the verumontanum on the rectal surface. It has a wide-open rounded lumen and appears to be distended. It possesses no glands. In the distal half there are in addition to the infolding on the rectal surface right and left lateral folds. These fall short of extending to the external urethral orifice, for the most distal portion of the urethra is flattened laterally and devoid of folds. In cross-section it has the form of a vertical slit and is easily recognized as the fossa navicularis. The distal half is provided with glands of Littre which are found, however, only on the pubic surface and directly in the midline. In all seven small gland buds are present, two of the largest ones alone showing any indication of developing lumens. Lichtenberg (16) reports the beginnings of glands in an embryo of 70 mm. on the lateral walls of the urethra. I am unable to make out any indications of beginning glands in this location at this stage.

In the glandar lamella of this specimen are seen the beginnings of a number of epithelial pearls, which become more numerous in older stages. Their significance is discussed in a succeeding portion of this paper.

Embryo no. 82, 88 mm. Length of urethra, 14.5 mm. The urethra of this embryo presents a curious picture as compared with my other specimens. Its general relations and curvatures are shown in figure 3, a graphic reconstruction made from serial sections. On the pubic wall are shown a number of small sinus

glands of varying size, some branched, and most of them bent bladderward. In addition to similar glands on the rectal surface are seen a number of cystic epithelial ducts, some of which are in no way connected with the epithelium of the urethra. In cross section the ducts have the appearance shown in figure 4. They lie in the connective tissue of the median raphe, and together form a linear series of disconnected tubules. In places they are provided with lumens of different shapes which are not continuous throughout each duct, but broken up into a series of

Fig. 3. Embryo No. 82, 88 mm. Long

Graphic reconstruction of a mid-sagittal section of the urethra to show the anomalous ducts found on the rectal surface of the urethra in this specimen.

irregular crevices. That these ducts are derivatives of the urethra cannot be questioned, for their epithelium is similar to that of it. At first glance they give the appearance of being cut off epithelial glands, but this view of their origin is untenable, not only because of their larger size, but because in certain places glands are seen arising from them. The explanation of their origin is found in a close examination of the rectal wall of the urethra, for in this region similar ducts are seen in the process of develop-

ment. Along the mid-line of the rectal wall of the urethra (fig. 4, *A*) there is a definite cord-like thickening of the epithelium. This cord, because of its thickness, cannot be regarded as a true fold, but is a definite proliferation of the epithelial cells. In places, such as is shown in the figures, it bears definite evidence of being cut off from the urethra by a constriction which is found close to the epithelium. In other places this cutting-off process is complete along part of the cord, while the remainder of it is still connected to the urethral epithelium. From such appear-

Fig. 4. Embryo No. 82, 88 mm. Long

Cross sections of the cavernous urethra to show anomalous cystic ducts. Level of sections shown in figure 3. × 90.

ances it seems safe to infer that those ducts which lie entirely free from the urethra have been cut off from it in a like manner at an earlier stage.

Why the formation of these peculiar structures and what their ultimate fate may be I am unable to state, since in no other embryo have I seen anything comparable to them. Nor have I been able to find any reference to similar structures in the literature. It is possible that certain of the anomalous conditions found in the adult, such as para-urethral ducts, may have a

similar origin. In this connection it should be mentioned that Ehrmann (7) explained the origin of para-urethral ducts as broken-off mucosal remains of the urethra, while Rona (24) believed them to be cut-off longitudinal folds. Neither of these authors, however, backed their opinions with embryological evidence. It is difficult to conceive, however, that the ducts which I have just described are para-urethral ducts in the making, for they show no external opening, and are far more extensive than the usually described para-urethral ducts.

In the bulbous portion of the urethra are seen the bilaterally placed Cowper's ducts, which, coursing bladderward, along the rectal wall of the urethra, break up into a number of branches. Unfortunately the whole of Cowper's glands and membranous urethra of this specimen were not available for study. Just behind the orifices of the ducts of Cowper's glands are seen a second pair of ducts, which, coursing parallel to the former, terminate in several small branches. These ducts lie entirely within the bulb of the urethra and are similar histologically to the ducts of Cowper's glands. Similar ducts were noted by Lichtenberg (16) in embryos of 70 and 210 mm., who regarded them as "accessory Cowper's glands."

The arrangement of the small sinus glands in this 88-mm. embryo deserves a word of mention. Corresponding exactly to the longitudinal outfoldings of the epithelial tube, the glands arise in perfect linear series. There can be distinguished, therefore, a row in the midline on the pubic surface, or mid-pubic row, a right and left latero-pubic row placed on either side of the former, right and left lateral rows situated definitely on the lateral wall, and the mid-rectal row mentioned above in connection with the curiously formed ducts.

Embryo no. 25, 90 mm. Length of urethra, 16 mm. This specimen shows nothing of special note but should be mentioned because of the tardiness of development of its urethral tract. Its curvatures and folds are essentially similar to those previously described. Its sinus glands, as well as the prostatic tubules, are fewer and smaller than at either the 88- or 75-mm. stage.

Embryo no. 204, 100 mm. long. This stage shows well developed sinus glands, but they are again less numerous than in the 88-mm. stage. The bulbo-urethral glands are approximately equal on the two sides and show a number of terminal branches. No accessory Cowper's glands are present.

Embryo no. 1018 Carnegie Collection, length 130 mm. Length of urethra, 21.5 mm. This stage has been studied largely by means of a wax reconstruction which is shown in figures 15 and 16. In many respects it represents a considerably more advanced state than those previously described and therefore deserves a more extended description.

The whole urethra presents the same general curvature as shown for the 65-mm. stage with the exception, however, that the proximal bend is more acute and the distal one less so. Moreover the pelvic urethra is relatively longer as compared with the phallic urethra than at the 65-mm. stage.

As seen in the figure, the prostatic urethra begins at the sharp constriction at the base of the bladder, is directed almost directly caudally, and terminates below the prostatic tubules by becoming the membranous urethra, the line of demarcation being indefinite. As in the above-described stage the prostatic urethra presents several small and irregular folds of its mucous membrane anteriorly, whilst posteriorly is the deep crista urethralis. Extending outward from the entire circumference of the prostatic urethra are the prostatic tubules. With but few exceptions, the prostatic tubules are directed bladderward, those of the lateral and posterior walls in addition winding spirally ventrally around the urethra. They are more numerous, larger, and show a greater degree of branching laterally and posteriorly, fewer, smaller, and less branched anteriorly. A definite grouping of the tubules in accordance with Lowsley's description is difficult and unsatisfactory, nor are the lobes of the prostate separable in any view of the model or from a study of the sections. An attempt to roughly group and count the glands of the various walls of the prostatic urethra has resulted in the following figures: anterior, eleven; right lateral, twelve; left lateral, ten; posterior above the ejaculatory ducts, three; posterior below the ejaculatory ducts, eighteen; making a total of fifty-four in all.

The membranous urethra is relatively short as shown in the figures and its boundaries not apparent from a study of the epithelial tube alone. It is smaller in caliber than the prostatic urethra and its mucosa thrown into a number of longitudinal folds, of which there may be distinguished three on the pubic wall, one on the rectal, and one each on the lateral walls. This portion of the urethra is without glands.

The proximal one-third of the cavernous urethra includes the so-called "bulbous urethra." This is somewhat larger in diameter than the membranous urethra, but shows the same infoldings of its epithelium. Of special interest are the glands of this region which are found on the rectal and lateral surfaces of the urethral tube. Extending from the rectal surface are Cowper's glands, the ducts of which arise at the anterior end of the bulbous urethra on either side of the median raphe of the bulb. Within the bulb are given off several branches which constitute the intrabulbar portions of the glands. Continuing through the bulb, each main duct pierces its connective tissue sheath, and immediately breaks up into a number of branches. The bodies of the glands, therefore, lie on the rectal side of the membranous urethra, but are separated from it by the sphincter muscle.

The glands on the lateral surfaces of the bulbous urethra, are three in number, two left and one right. All three are of the same character, the ducts in their proximal portions extending distally, then curving backward are directed bladderward. The gland on the right is larger than either of those on the left and shows several small branches.

The identity of these glands is by no means certain. That they are not constantly present is apparent for in only two other specimens have I found glands in a similar position. It is probable that they correspond to the glands which Motz and Batrina (18) have described under the term "glands of Littre." These authors figure a microscopic section of a compound, tubulo-alveolar, mucous gland lying dorsal to the membranous urethra, and diagrammatically, a zone of glands around this portion of the urethral tube.

The cavernous urethra distal to the openings of the ducts of Cowper's glands presents a number of longitudinal folds, which,

although not absolutely regular throughout, are arranged in general as follows: a median fold on the rectal, paired folds laterally, and a pair of folds on the pubic surface. The anterior three-fifths of the cavernous urethra shows numerous elongated Littre's glands, many of which are branched. Most of these are directed bladderward, but a few are found which extend perpendicularly to the long axis of the urethra or are bent so that they point toward the glans. They are arranged in rows, the rows corresponding to the epithelial ridges between the mucosal folds. There are to be distinguished a median row of glands on the pubic surface, eleven in number, including the largest of the Littre's glands. On either side of the median row, still on the pubic surface, is another row, the right containing eleven, and the left nine glands. In addition there is a row on each lateral surface, the right containing four and the left three glands. The latter are the smallest. Not a single gland was found on the rectal surface of this portion of the urethra. A few of the largest of the urethral glands show beginning lumens. but the majority are still solid epithelial stalks.

The anterior part of the cavernous urethra, that is, that part which lies within the glans penis is flattened laterally and is without folds or glands. It opens to the outside on the rectal surface of the tip of the glans by a crescentic-shaped opening.

Of special interest at this stage is the glandar lamella, for one sees a marked change in its shape and position. If it be compared with that at 65 mm., (fig. 13), it will be seen that its attachment to the epithelial covering of the penis lies nearer the tip of the glans and is directed longitudinally with the penis rather than transversely. This change in position is brought about by an apparent shifting, the nature of which is discussed in a later portion of this paper.

Embryo no. 324, 147 mm. Length of urethra ca. 32 mm. From this embryo the whole of the urethra with the surrounding structures was carefully dissected out and cut into five blocks of about equal length. Each block was then embedded in paraffin and cut in serial sections.

The prostatic urethra shows considerable advancement over that of the previously described stage. Its tubules are longer,

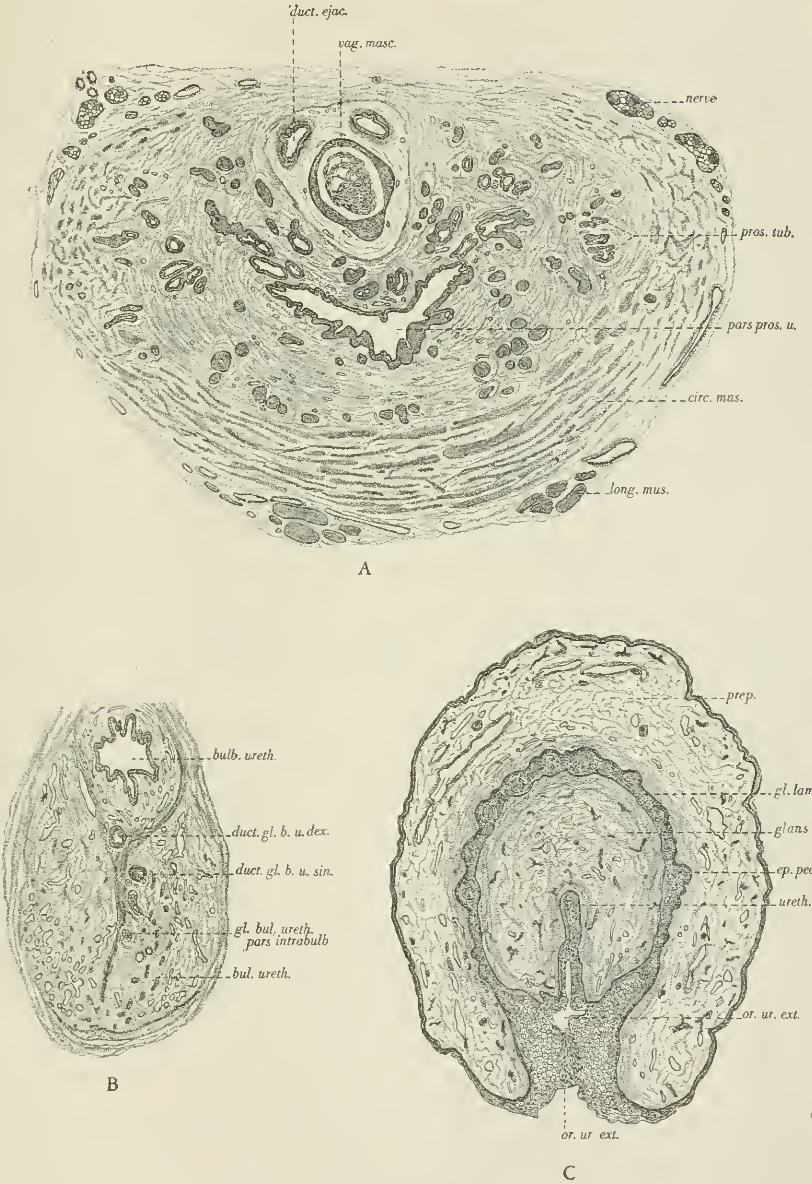


FIG. 5. EMBRYO NO. 324, 147 MM. LONG

A, section, showing prostate, with anomalous cystic vagina masculina. *B*, section, showing bulb of urethra with main ducts and intrabulbar portion of Cowper's gland. *C*, section, through glans and prepuce. × 17.

more branched, and the lumens better developed, yet in no place is there definite evidence of secretory activity. The tubules of the anterior wall are the smallest, those of the posterior and lateral walls, the largest. The tubules of the middle lobe are more numerous and larger than in the above-described specimen. Of special interest in this portion of the urethra is the utero-vaginal canal or vagina masculina. This structure (fig. 5, *A*) has become cystic and appears as a pyriform vesicle filling the upper part of the verumontanum. Its diameter is about one-third that of the transverse diameter of the urethra itself. Its walls are thick, being composed of a stratified squamous epithelium of from ten to fifteen layers of cells. The lumen is large and contains numerous desquamated epithelial cells.

The membranous urethra is smaller in caliber than the prostatic and its epithelium thrown into a number of irregular longitudinal folds of which may be recognized two pairs on the pubic surface, one laterally, and a single fold on the rectal surface. The epithelium is thinner than that of the prostatic urethra and possesses no glands. Surrounding the membranous urethra is a definite band of muscle tissue which is the direct continuation of that of the prostate.

As the urethra pierces the proximal surface of the bulb it bends sharply toward the pubis and becomes the cavernous urethra. There is, however, no essential change in the epithelial tube, although the mucosal folds become perhaps even more irregular. In the bulb only Cowper's glands are to be found. These arise well forward in the bulb from the rectal surface of the urethra by means of two elongated ducts, the left of which extends further distally than the right. Both ducts extend bladderward parallel to the surface of the urethra, and, reaching the dorsal surface of the bulb, break up into a great number of branches. In passing through the bulb, the ducts give off a few branches which redivide to form the intrabulbar portions of Cowper's glands, the left of which is shown in figure 5, *B*. The terminal branches end in definite alveoli. The epithelium of the ducts is for the most part composed of two to three layers of granular cuboidal cells, but there are also to be found irregularly distributed patches of

clear mucous cells. Similar patches of mucous cells are more abundant in the alveoli, but by no means do they constitute the whole of the alveolar epithelium. Glands on the lateral surfaces of the bulbous urethra, such as were found in the preceding stage, are absent in this specimen.

Distal to the openings of Cowper's ducts the cavernous urethra shows no marked changes in form or structure. While the proximal one-third is devoid of glands, the distal two-thirds shows them in great abundance (fig. 10, *B*). They are most numerous on the pubic surface, but they are also to be found on the lateral and rectal surfaces. Many of the glands extend completely through the substance of the corpus cavernosum urethrae and lie in contact with the connective tissue sheath which surrounds this structure. The glands are now provided with lumens except in their smaller branches, and are lined with an epithelium composed of coarsely granular cuboidal cells. In several of the glands one sees for the first time small patches of clear secretory cells of the mucous variety.

Toward the distal end of the cavernous urethra the epithelial tube becomes flattened vertically and thrown into a number of irregular folds. As the fossa navicularis is reached the lateral outfoldings of the tube terminate rather abruptly, the urethra increases in its vertical diameter and becomes flattened laterally. This flattened portion, the fossa navicularis, is provided with a thickened stratified squamous epithelium and is without folds or glands (fig. 5, *C*). One sees, however, at the proximal end of the fossa on its dorsal wall, a solid bud-like epithelial sprout, directed bladderward. This structure, unquestionably a lacuna magna, is not constantly present in all embryos. It has been found and figured by Broman (4) in an embryo of 17 mm.

The glandar lamella of this specimen (fig. 5, *C*) is again deserving of a word of mention. Its line of attachment to the epithelium covering the penis is now found to be close to the external urinary meatus. At irregular intervals in its thickened stratified squamous epithelium are found definite rounded swellings of various sizes, the so-called "epithelial pearls." These structures furnish the means by which the glandar lamella is split into its

two ultimate layers, one of which covers the inner surface of the prepuce and the other the glans penis.

Embryo no. 1049, Carnegie Collection, 171 mm. Of this embryo only the distal portion of the pars cavernosum urethrae and the proximal portion of the pars prostatica were available. The former was studied by means of a wax reconstruction which is shown in figure 17. At the distal end of the model, which again represents only epithelium, are seen the epithelial layers of the prepuce, the glandar lamella of which serves as the common covering for prepuce and glans. Its epidermal attachment is now located along the external urinary orifice. Beyond the presence of epithelial pearls there is as yet no indication of the splitting process which later divides this epithelium into its two layers. The fossa navicularis which is again flattened laterally, presents nothing of especial note. No lacuna magna is present. Proximally the fossa passes over into the broader portion of the pars cavernosum without sharp demarcation. This portion is distended, folds of the mucosa being absent except for one shallow infolding along the rectal wall. The walls of the urethra are covered by a large number of branched sinus glands, of which most are directed bladderward, a few extending vertically to the long axis of the urethra or bending distally towards the glans penis. The arrangement of the glands into definite rows is of interest in the absence of mucosal folds, for it points to the existence of potential folds which, because of the distention of the urethra, are obliterated. There is seen a row of ten glands along the midline of the pubic surface which contains the largest and most branched glands, a row on each right and left sides, containing sixteen and nine glands respectively, and a row of glands along each right and left margin, more highly developed on the left than on the right and containing five and fifteen glands respectively. In addition there is a row of glands along the midline on the rectal surface, not shown in the figure. The latter, which are not highly developed, appear as short, solid epithelial outgrowths and are directed toward the glans penis.

Embryo no. 332, 190 mm. Length of urethra ca. 38 mm. From this specimen the whole of the urethra with the adjoining tissues

was dissected out, cut in seven segments and embedded in paraffin. All of the distal segment was cut in serial sections, but from the remaining segments only enough sections were taken to study the urethra at various levels.

The two proximal segments include the prostatic urethra. The prostate again shows no noteworthy changes. The prostatic tubules are embedded in a mass of connective tissue. On the anterior and lateral walls of this mass are the circular muscle fibers, the downward continuation of which gives rise to the sphincter of the membranous urethra, as shown by Wesson (26).

The membranous urethra is again smaller in size than the prostatic urethra and its mucosa is thrown into large longitudinal folds. The epithelial tube is surrounded by a very vascular tunic and this in turn surrounded by the circular fibers of the sphincter muscle. Dorsal to the membranous urethra, but separated from it by the sphincter muscle are the extra-bulbar portions of Cowper's glands. These, lying one on either side of the median raphe, show numerous ducts and alveoli, both of which again contain many mucous secretory cells in their epithelia.

The cavernous urethra begins at the entrance of the urethra into the bulb. The mucous membrane shows longitudinal folds similar to those of the membranous urethra. Its only glands are Cowper's, and these show a marked variation from the normal. One duct, that of the right side, serves both glands. Within the bulb this single duct gives off several branches which, extending to the right side, constitute the right intrabulbar gland. The left intrabulbar gland possesses but a single duct which crosses the median raphe to join the main duct of the right side. The single duct of the right side continues through the bulb, but upon reaching its upper end gives off a rather large duct which again crosses the median line to the left side. These two ducts then divide into branches which constitute the right and left extrabulbar portions of Cowper's glands respectively.

The remainder of the cavernous urethra shows two longitudinal folds on the pubic wall, one on each lateral and three to five small and less distinct folds on the rectal wall. Although these folds are continuous, they show several irregularities and in places

small additional folds are found between the larger ones. Immediately distal to the ducts of Cowper's glands the cavernous urethra is entirely devoid of glands. The glands of Littre, which are confined to the anterior three fifths of the cavernous urethra, become larger as the distal end of the urethra is approached. They are again arranged in longitudinal rows of which there are six (fig. 10, *C*). Many of these are branched but a few are still solid epithelial outgrowths. The latter undoubtedly represent newly developed glands which have sprouted from the urethra in between the older ones. The larger glands are provided with lumens and their ducts and alveoli contain patches of secretory cells. The younger glands are both without lumens and secretory cells.

Just before the fossa navicularis is reached, the urethra becomes flattened vertically and while folds are present, they are inconspicuous. The fossa itself is flattened laterally; it is similar to the last described stage in possessing no evidence of a lacuna magna. In the region of the external urethral orifice is seen a beginning of a longitudinal splitting of the glandar lamella. The splitting, however, is not extensive, and is confined to the immediate vicinity of the orifice.

Embryo no. 7, 220 mm. Length of urethra ca. 42 mm. In this specimen the urethral tube is essentially similar to that of the above-described embryo. The prostatic tubules, especially laterally and posteriorly, are greatly elongated and branched, and pierce deeply into the surrounding tissue. The membranous and cavernous urethrae are flattened vertically and the mucosal folds are quite irregular in position and size throughout. Glands of Littre are present in the pars cavernosum except for a small portion at its proximal end. They are again most numerous, larger, and more branched on the pubic surface; on the rectal surface they are extremely few and small. All, except the smallest glands are provided with lumens and contain secretory cells.

The two ducts of Cowper's glands are seen arising side by side from the rectal wall of the bulbous urethra. The left duct gives off several branches shortly after its origin from the urethra, which, redividing, forms a portion of the intrabulbar gland.

This lies for the most part just to the left of the median septum of the bulb, but a few of its alveoli lie to the right of or in the median line. Further out along the main ducts are additional intrabulbar branches from both right and left ducts. The extra-bulbar portions of Cowper's glands are of about equal size, are situated upon the cephalic wall of the bulb, and are separated from the membranous urethra by the sphincter muscle. They show repeated divisions, the branches terminating in alveoli. Both ducts and alveoli contain the typical mucous secretory cells lying in groups, the remainder of the epithelium being composed of cells with a granular protoplasm. Certain of the ducts, as shown in figure 6, have become cystic.

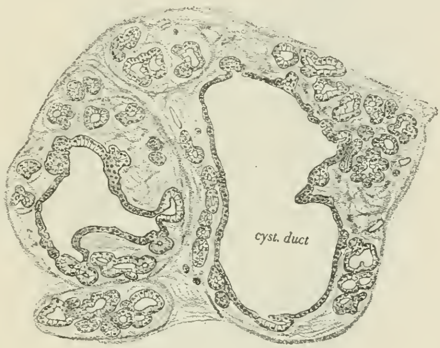


Fig. 6. Embryo No. 7, 220 mm. Long

Section through small portion of Cowper's gland to show cystic condition of the ducts. × 50.

Of unusual interest in this specimen are three glands which lie in relation to the bulbous and membranous urethrae (fig. 8). Two of these arise from the lateral walls of the bulbous urethra proximal to the orifices of Cowper's ducts. Their ducts are directed bladderward, one on either side of the midline, paralleling those of Cowper's glands. Passing through the bulb, they lie lateral to the membranous urethra and break up into a number of branches within the vascular connective tissue surrounding the epithelial tube (fig. 7). Wholly within the membranous portion of the urethra, a similar gland, though smaller in size, arises

from the rectal surface of the epithelial tube, and extending toward the right side, breaks up into branches and alveoli. Some of the branches of these glands are long and penetrate the muscular fibers of the M. sphincter membranaceae urethrae. All three glands are of the branched tubulo-alveolar type and contain numerous areas of mucous cells in their ducts and alveoli, and although smaller, are similar histologically to Cowper's

FIG. 7. EMBRYO NO. 7, 220 MM. LONG

Section through membranous urethra to show glands of this portion of the urethra. Compare with figure 8. × 50.

glands. Like the latter, their bodies lie behind the membranous urethra. They are, however, separated from Cowper's glands by the sphincter muscle. Their position is similar to those glands which Motz and Batrina (18) have described as "glands of Littre."

The fossa navicularis of this specimen presents on its pubic margin a definite lacuna magna. It is composed of granular epithelial cells, is without a lumen, and measures 0.28 mm. in length

and 0.065 mm. in diameter at its base. The transition from stratified squamous to columnar epithelium takes place a short distance proximal to the lacuna magna, the fossa epithelium disappearing first on the rectal wall, then on the pubic, and persisting farthest proximally on the lateral walls of the urethra.

The attached margin of the glandar lamella is again found along the external urinary orifice. The lamella itself is somewhat thinner and contains fewer epithelial pearls than in the last-described stage. It presents along its attached margin a longi-

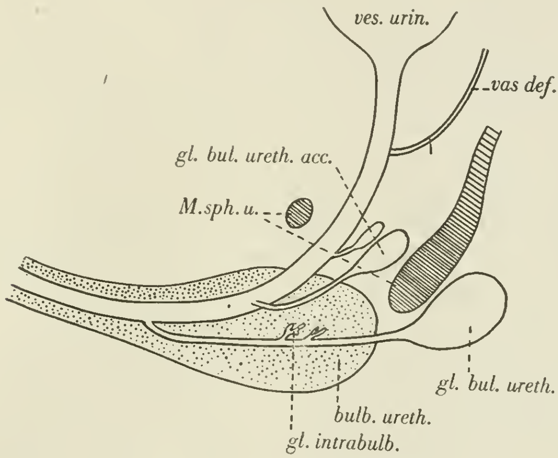


FIG. 8. EMBRYO No. 7, 220 MM.

Diagrammatic drawing showing position of glands of bulbous and membranous urethrae.

tudinal splitting, so that the tip of the glans and the end of the prepuce have, at this stage, their own individual coverings.

Embryo no. 48, 270 mm. Length of urethra ca. 65 mm. The urethra of this specimen was cut into eleven segments and the segments cut serially. From the sections certain regions were selected and modelled in wax as shown in plate 4.

In the model shown in figure 23, is represented one of the lowermost of the lateral prostatic tubules, the numerous branches of which penetrate deeply into the surrounding muscular tissue. The ducts of two posterior glands are also shown in the figure.

Higher up in the prostate the glands are larger and more numerous, and extend in all directions from the urethra. Except for their greater size and greater degree of branching they are essentially similar to those shown in figure 16.

In figure 22, a segment from the bulbous urethra, are seen two pubic, two rectal and two lateral folds, in addition to several smaller secondary folds. Glands are entirely lacking. The ducts of Cowper's glands, which course along the rectal wall of the urethra (not figured) are large and their walls thrown into small longitudinal folds. The epithelium of the ducts contains patches of secretory cells, which increase in number when followed toward the bodies of the glands. In many places these patches of mucous cells form small lateral outpocketings (alveoli) along the ducts, as shown by Lichtenberg (16). Intrabulbar branches were found arising from the left duct only. They likewise contain mucous cells lining definite alveoli. The extrabulbar portions of Cowper's glands show nothing of interest beyond an increase in size. Other glands, such as were found in a preceding stage, are entirely absent from the bulbous and membranous portions of the urethra of this specimen.

In figure 21 is shown a segment of the cavernous urethra immediately distal to the bulb. Although broader and flatter than the bulbous urethra, its mucosa shows corresponding folds. No glands are to be found in any of the sections of this segment.

The model shown in figure 20, taken from about the middle of the cavernous urethra, shows three distinct folds on the pubic surface and two on the rectal, in addition to a number of small secondary folds. Glands of Littre are now conspicuous. They extend through the very vascular tissue of the corpus cavernosum urethrae to reach its fibrous sheath. The ducts of the glands with but a single exception are again directed bladderward, but the terminal branches extend in all directions. The ducts are lined for the most part with clear mucous cells. Some of the branches have definite terminal swellings (alveoli) and these likewise are lined with mucous cells. A number of the glands are still unbranched and solid, representing undoubtedly, newly formed glands.

A short distance behind the fossa navicularis (fig. 19) the urethra is seen as a vertically flattened tube, having one large outfolding on its pubic wall and a number of secondary folds. A few glands are seen but they are small and not all are branched. All are directed bladderward and lie close to the urethral epithelium. Several small bud-like glands on the pubic wall contain mucous cells, but the remaining ones are not only lacking in secretory cells, but are only partially provided with lumens.

The fossa navicularis, a model of which is shown in figure 18, is again flattened laterally. Its epithelium, stratified squamous in type, is composed of from ten to thirty layers of polygonal cells. The inner surface of the epithelium is smooth, i.e., without folds. Its outer surface, however, presents a number of oblique or longitudinal ridges which are larger near the rectal margin of the fossa. On the pubic surface of the fossa is seen a large lacuna magna, which measures 0.62 mm. in length and has a diameter of 0.22 mm. at its base. It is likewise composed of polygonal cells which surround a very small centrally-located lumen. The lacuna magna is not located at the extreme proximal end of the fossa navicularis, for the stratified squamous epithelium continues proximally some little distance beyond it. The transition of the stratified epithelium of the fossa to that of the columnar type takes place, when followed proximally, first on the rectal wall, next on the pubic wall, and lastly on the lateral walls.

The glandar lamella shows considerable thickening again. It contains numerous epithelial pearls, many of which are greatly enlarged and form bulgings on the preputial surface of the epithelium, giving it an undulating appearance. No evidence of a splitting of the lamella could be found.

The epithelium of the whole urethra of this specimen is of especial interest. With the exception of that of the fossa navicularis, the epithelium is stratified columnar, the cells of which are coarsely granular. However, in the whole of the cavernous urethra and to a less degree in the membranous and prostatic portions are found large numbers of clear polygonal cells interspersed among the more granular cells. These cells are large and vesicu-

lar; the cystoplasm is clear and the nuclei pyknotic, so that they give the picture of the more superficial of the stratified squamous cells of the fossa navicularis. They are usually arranged in groups or patches, but are also found singly. Occasionally small groups are found completely embedded in the epithelium, but more often they lie on the surface. Similar cells are found in the prostatic tubules, where, in many instances, they entirely fill up the lumen.

Embryo no. 12, 310 mm. (stillborn). This embryo shows very little of importance beyond a slight increase in size of its various structures. Of special interest, however, is the cystic condition of the right Cowper's duct. This duct is apparently occluded near its outlet and its terminal portion has become greatly distended.

No glands were found in relation to the membranous urethra but a few small subepithelial gland alveoli are present on the various walls of the upper portion of the bulbous urethra. A lacuna magna was not found.

The prepuce shows a higher degree of development than in the previous stage. The splitting of the glandar lamella has reached a more advanced stage and the cleft thus formed, as well as the external urinary orifice, is filled with desquamated epithelial cells. Epithelial pearls are again present, but they are not as large or as numerous as in the preceding embryo.

Embryo no. 9, 320 mm. (stillborn). This specimen is of interest in that it presents another instance in which the ducts of Cowper's glands are anomalous. Only the right duct is in this instance connected with the urethra. After giving off several blind ducts, the right duct gives off a larger duct, which crossing to the left of the median line, continues to the body of the left gland. The left duct, however, is occluded at the point where it joins the right, and a large portion of it is greatly distended. No other glands were found in the region of the bulbous or membranous urethrae.

The glands of Littre, confined again to the anterior two thirds of the cavernous urethra, are numerous and large on the pubic wall, few and small on the lateral walls, and entirely absent on

the rectal wall. They show numerous patches of mucous cells in their ducts and alveoli.

At the posterior end of the fossa navicularis, there is a well-defined lacuna magna on the pubic surface. It measures 1.4 mm. long and 0.5 mm. in breadth at its base. Its epithelium is of the stratified squamous variety and it contains a small though distinct lumen. Secretory cells are entirely lacking in its epithelium.

Fig. 9. Specimen No. 9, 320 mm. Long (Stillborn)

Section of bulb of the urethra to show cystic condition of duct of left Cowper's gland. × 17.

The glandar lamella shows a greater degree of splitting than in any of the previously described stages, but its division is not yet fully completed. Many of the epithelial pearls have increased in size, their centers have undergone swelling and degeneration, the cavities thus formed have united, thus aiding in the splitting process. Large numbers of desquamated epithelial cells fill the space between the prepuce and glans, and occasionally large whorls of epithelial cells, the degenerated epithelial pearls, are found within the space.

Postnatal stages. In two postnatal stages, one two and one-half months (no. 5939) and the other twenty months (no. 5935) the urethra and its glands, have, except for size, virtually reached

the adult condition. The prostatic urethra, rather small and triangular in shape above the verumontanum, becomes larger and crescentic when this structure is reached. In addition to the verumontanum, there are a number of smaller longitudinal folds of the mucosa, especially on the pubic wall. The epithelium of the prostatic urethra varies in thickness in various portions, being composed of from three to six layers of cells. The

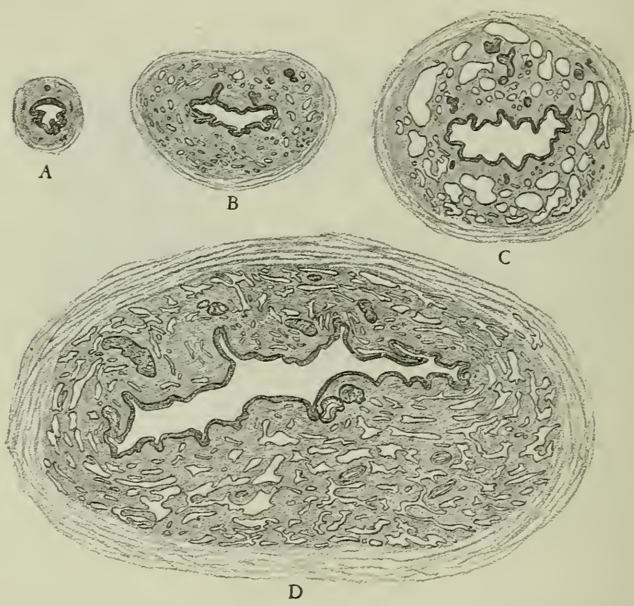


Fig. 10. Four Cross Sections of the Urethra to Show Graphically the Growth of the Cavernous Urethra, the Glands of Littre, and the Corpus Cavernosum Urethrae

A, 75 mm. embryo; *B*, 147 mm.; *C*, 190 mm.; *D*, 2½ months, postnatal

superficial layer of cells, for the most part truly columnar in shape, are in certain areas cuboidal or even squamous. The prostatic tubules, are similarly lined with a stratified columnar epithelium. Their smaller branches, however, are lined with an epithelium of one to two layers of cuboidal cells. The tubules are again longest and most numerous posteriorly and laterally, smallest and fewest anteriorly. A well defined middle lobe group

of gland tubules is demonstrable but a division into posterior, lateral, and anterior lobes is not possible from the sections.

The membranous urethra, the upper limit of which is ill-definable, is only slightly smaller in diameter than the prostatic portion. Its mucous membrane is thrown into four large folds with several smaller folds between them. The epithelium is composed of three to five layers of cells, the surface cells of which vary from low columnar to squamous. The latter, however, are more abundant in the prostatic urethra. No glands were found in relation to the membranous urethra.

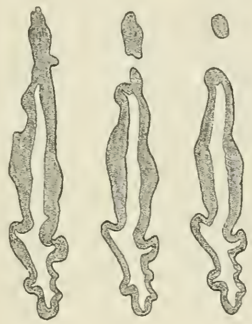


Fig. 11. Embryo No. 7, 220 mm.

Three sections of fossa navicularis to show lacuna magna. *A*, section 142; *B*, 144; *C*, 150. × 45.

In the bulbous urethra five large folds and numerous small secondary ones are found. The epithelium is stratified columnar in type, and composed of three to four layers of cells. Cowper's glands alone were found in this portion of the urethra of both specimens. Their ducts are large and show several small longitudinal folds. The epithelium lining them is stratified columnar and shows numerous patches of secretory cells amongst the more granular ones. The intrabulbar portions of the glands are present and show numerous branches terminating in alveoli. The extrabulbar portions of the glands are much larger than the intrabulbar, are situated dorsal to the membranous urethra, but separated from it by the sphincter muscle.

The cavernous urethra of both specimens shows again several irregular folds, there being no uniformity in their position. In one case the urethral tube is flattened vertically, in the other it is distended but not to the extent as to eradicate the larger urethral folds. The epithelium of the cavernous portion of the urethra is of the stratified columnar type. The small urethral glands are similar in distribution, arrangement, and structure to those of the previously-described stages. In one specimen they are present on the rectal wall, in the other absent. The glands are greatly branched and contain numerous cuboidal secretory cells in their ducts and alveoli. In many instances they penetrate the entire thickness of the corpus cavernosum urethrae and lie in close relationship to its connective tissue sheath.

Lacunae of Morgagni, such as were found by Lichtenberg in the urethra of a two-year old boy, I have found in the twenty months specimen only. I am, however, unprepared to assert their absolute absence in the two and one-half months specimen, since the whole of the urethra was not sectioned and since no models were made. Lacunae magnae were absent in both specimens.

SUMMARY AND CONCLUSIONS

The male urethra is composed of two portions, the true urethra which lies above the openings of the genital ducts, and the urogenital sinus which lies below. Of these the urogenital sinus becomes greatly elongated and forms by far the largest portion of the urethra. A division of the urogenital sinus into pelvic and phallic portions, such as Felix (8) has described for the early stages, is of descriptive value, but has no true embryological significance. Other divisions of the urethra into prostatic, membranous, and cavernous portions, or anterior and posterior urethrae, are likewise arbitrary divisions and have no importance from an embryological view-point.

Prostatic urethra. The prostatic urethra is composed of the whole of the true urethra and a portion of the urogenital sinus. Its upper limit is the neck of the bladder, its lower limit being not sharply definable in embryological material. It comprises

the broadest portion of the urethral tract and is the most constant in shape. With the exception of a small portion proximally, the prostatic urethra is crescentic in cross section, its concave surface facing the rectum. The large longitudinal fold which gives to the urethra its characteristic crescentic shape is the crista urethralis or verumontanum, a structure which is constantly present. Through it the fused Müllerian ducts, the Wolffian ducts and numerous tubules of the posterior and lateral portions of the prostate reach the urethra. On the anterior and lateral walls of the prostatic urethra smaller and less constant longitudinal folds are found.

The epithelium of the prostatic urethra is more variable in type than that of any other portion of the urethra. In the early stages it is stratified, being composed of from three to five layers of polygonal or cuboidal cells. In the later stages it varies in thickness from two to six cells, the superficial layer varying all the way from tall columnar to pavement in shape. The areas of pavement cells are more abundant on the verumontanum but small patches are interspersed in various parts of the urethral wall between areas of cuboidal or columnar cells. The cells are coarsely granular, stain intensely and show definite cell outlines in most places.

Prostate. The observations which I have made on the development of the prostate may be summed up in few words. The prostatic tubules were first observed in an embryo of 55 mm. crown-rump length. They begin, as described by Lowsley (17) and others, as solid epithelial sprouts from the prostatic urethra. These arise at about the same time from the posterior, lateral and anterior walls of the urethra. They penetrate the condensed mesenchma in which myoblasts are demonstrable. The tubules grow rapidly in length, soon acquire lumens and begin to branch. In the early stages the glands of the anterior, lateral and posterior walls are separable into groups, which, according to Lowsley, give rise to the various lobes of the prostate. With the exception of the middle lobe, which is formed by those posterior tubules which lie above the ejaculatory ducts, I have been unable to make out a division into lobes. The branches of the posterior, lateral, and anterior tubules lie in close approximation with one another, with

no suggestion of definite septa between them. The epithelium of the prostatic tubules is quite similar to that of the prostatic urethra, being composed of two to four layers of low columnar, cuboidal or polygonal cells.

No other glands are present in the prostatic urethra. The statement which one occasionally encounters that the urethral glands or glands of Littre are present in this portion of the urethra is, according to my observations, without foundation.

Membranous urethra. The membranous urethra comprises the middle portion of the pars pelvina of the urogenital sinus. In the early stages its limits are not marked and only become so with the formation of the M. sphincter urethralis membranacea and the inferior layer of the pelvic diaphragm. The upper limit is never clearly marked for the muscle fibers of the sphincter muscle are continuous with those of the prostate, as recently shown by Wesson (26). The division between prostatic and membranous urethrae may best be defined as the point where the lowermost prostatic tubules leave off.

The mucosa of the membranous urethra is thrown into several large longitudinal folds, usually four to six in number. Although their position is not constant, there is usually one large fold on the rectal surface which is the direct continuation of the verumontanum. In the older stages smaller folds are present between the larger ones. The epithelium is essentially similar to that of the prostatic urethra, but contains areas of squamous cells which are larger in size and more numerous. The epithelium rests upon a definite basement membrane, surrounding which is a connective tissue which is rich in its vascular supply, so that it resembles one of the cavernous bodies. This in turn is surrounded by the fibers of the sphincter muscle.

Glands of the membranous urethra. Glands of the membranous urethra are sometimes present but are by no means found constantly. They may have their origin from either the bulbous or membranous urethra. In the thirteen specimens I have examined which were old enough to show them, the glands were found in only three. The glands attain considerable size, branch several times, and become compound tubulo-alveolar in type. Their

ducts arise from either the rectal or the lateral walls of the urethra. They are few in number, three being the most I have found in any one specimen. Histologically they are similar to and I believe closely related with the large bulbo-urethral glands (Cowper's).

Glands of the membranous urethra were first described by Littre in 1700, who states (cited from Jarjavay):

> La deuxième glande, placée entre les deux membranes de l'urètre immédiatement apres la glande prostate du côté du glande, est une glande qui n'a point de nom, parce qu'elle n'a point encore été décrite. Cette glande est d'une couleur de rouge foncé; elle forme autour de l'urètre une espece de bande unie, large d'un pouce et épaisse de deux lignes, et perce la membrane intérieure de l'urètre dans toute sa circonférence par un grand nombre de conduits excrétoires, qui versent dans ce canal la liqueur, que la glande filtre.

Jarjavay (12), in his classical study of the male urethra, says in regard to Littre's description of the glands of the membranous urethra:

> Evidently Littre has taken for a gland the muscular coat which surrounds the urethra in this segment of the canal. The error was induced by the presence of the numerous orifices on the internal face of the mucosa in the corresponding part, the orifices which Manget did not see, which Morgagni said did not always exist, and which without doubt were not discovered by numerous authors who have kept silent on this subject. It is certain that they exist more or less numerously, more or less visibly, and that their series continues a little on the superior wall of the prostate, which without doubt have led Terraneus to consider them as an appendix of this gland.

Robin and Cadiat (23) have also described glands in the form of follicles throughout the whole length of the urethra in the male. Motz and Batrina (18) figure a zone of glands surrounding the membranous urethra in man, and believe they are the glands which Littre originally described. On the other hand, Lichtenberg (16) makes no mention of the glands in the membranous urethra of a two year old boy which he described so thoroughly. He has, however, described certain glands in his embryological

material which are situated in the bulbous urethra proximal to the ducts of Cowper's glands. These glands have their origin on the rectal surface of the urethra and are similar histologically to Cowper's glands. Because of their position, their structure and close relationship to Cowper's glands, Lichtenberg has designated them as "accessory Cowper's glands." Such glands he did not find constantly, but only in embryos of 70 and 210 mm.

The significance of the glands of the bulbous and membranous urethrae which I have found and described above is apparent from a study of their histology. As stated before they are the exact replicas of Cowper's glands and therefore must bear a close relationship to these structures. Those of the bulbous urethra are so closely related in shape, position, direction and structure that there can be no question but that Lichtenberg has most appropriately termed them "accessory Cowper's glands." I would also include under this term the few glands of the membranous urethra as well. This view will appear more justifiable when it is recalled that the division of the urethra into membranous and cavernous portions is purely artificial and is without true embryological significance. The fact that Cowper's glands are separated from the membranous urethra by the sphincter muscle, whereas the accessory glands lie within the mucosa of the urethra, is, in my opinion, a relationship of no consequence.

With regard to the descriptions of Littre and Jarjavay, I am inclined to believe that these authors probably saw the lowermost prostatic tubules, and that the view of Terraneus (cited from Jarjavay) who considered them as an appendix of the prostate, is essentially correct.

Cavernous urethra. The cavernous urethra is derived exclusively from the urogenital sinus and includes the lower portion of the pars pelvina and the whole of the pars phallica. In its course it lies entirely within the bulb and the corpus cavernosum of the urethra, terminating in the glans penis.

The so-called "bulbous urethra," a division not recognized in the B.N.A., includes that portion of the urethra immediately distal to the membranous portion, lying wholly within the bulb of the urethra. In this region the urethra presents its character-

istic ventral curvature. The bulbous urethra is essentially similar to the membranous urethra, containing a similar epithelium and presenting almost identical folds of its mucous membrane. Extending from the rectal surface of the bulbous urethra are the two bulbo-urethral glands. The beginnings of these glands are already present in the youngest stage I have described (55 mm.), in a stage in which the bulb itself is not apparent. Eggerth (6) reports their presence in an embryo of 30 mm. They are at first solid rod-shaped structures. They are directed bladderward lying on either side of the median line, and coursing parallel to the epithelial tube of the urethra. Their ducts grow rapidly in length, soon acquire lumens, and pierce the proximal sheath of the bulb. The extra-bulbar branches are first to form. Their beginnings were found in an embryo of 75 mm. Intrabulbar branches were first seen at 130 mm. The former comprise by far the greater portion of Cowper's glands, pushing their way up alongside the urethra, but separated from the membranous urethra by the sphincter muscle. The intrabulbar branches are few in number and entirely confined to the bulb. Histologically Cowper's glands are of the compound tubulo-alveolar variety, both ducts and alveoli containing numerous mucous cells. Those of the ducts, including the main ducts, are arranged in scattered groups, which may take the form of an alveolus or may remain flush with the surface of the duct, as was well shown by Lichtenberg. Because of the secretory character of the ducts, Lichtenberg insists that these should not be considered purely as excretory ducts, but as integral portions of the glands themselves.

Anomalies of Cowper's glands are not uncommon in the adult, so it is not surprising to find them in fetal stages. Out of fifteen embryos, ranging from 55 mm. in length to birth, anomalous conditions were found in three. In specimens of 190 and 320 mm. the duct of the right side alone reached the epithelial tube of the urethra, the left duct being a branch from the right and crossing the midline to reach its gland body. In specimens of 310 and 320 mm. the right and left ducts respectively were occluded at their outlets, and a cystic condition of their terminal portions was found as the result of distention.

Mucosal folds. Distal to the bulbous portion, the cavernous urethra presents a number of large longitudinal folds of its mucous membrane similar to those of the bulbous and membranous urethrae but somewhat more constant in position and form. The first definite folds are seen in embryos of 55 and 65 mm. and are confined to the distal two-thirds of the cavernous urethra. They are three in number, a right, a left, and a rectal. These gradually extend proximally through the whole of the cavernous urethra and to them are added two folds on the pubic surface which are quite definite at 120 mm. These five folds are found in older embryos with few exceptions, but between the larger folds are added secondary folds, which in certain instances attain the size of the primary ones. In cases where the urethra is distended, the folds largely or wholly disappear, depending upon the degree of distention. In other cases, where, owing to compression, the urethra is flattened, the position of the folds is not clearly determinable.

In his study of the folds of the urethra of a boy two years old, Lichtenberg (16) has described four large primary folds, and in addition folds of the first, second, and third orders, the latter being merely thickenings of the epithelium forming ridges on the inner wall without corresponding depressions on the connective-tissue surface. In my specimens I find a certain resemblance to the condition figured by Lichtenberg, but the similarity is neither close nor constant.

The epithelium of the cavernous urethra is stratified columnar, its thickness varying from two to five layers of cells in different specimens and in different places in individual specimens. Occasionally one sees small areas where the surface epithelial cells are of the polygonal or squamous type, these being particularly abundant in my 270 mm. specimen.

Urethral glands. The urethral or small sinus glands, glands of Littre, have already made their appearance in an embryo of 55 mm. At first they are small knob-like processes of the urethral epithelium, but rapidly grow to assume a tubular form. When they attain a certain degree of development they begin to branch and to acquire lumens, first in their ducts and later in

their branches. The terminal branches form alveoli similar to those of Cowper's glands, the cells of which become clear and of the mucous type. Like the ducts of Cowper's glands the ducts of the urethral glands likewise contain scattered groups of secretory cells in their epithelia. The first glands to form are those in the midline on the pubic surface of the urethra. These begin to branch and acquire lumens at 88 mm. and mucous cells make their appearance at 147 mm.

The glands are always confined to the anterior two-thirds or one-half of the cavernous urethra, beginning just behind the fossa navicularis and never extending as far proximally as the ducts of Cowper's glands. They are arranged in longitudinal rows corresponding to the furrows between the mucosal folds. There are to be distinguished a mid-pubic row, two lateral pubic rows, paired lateral rows and a mid-rectal row, the latter of which is not constantly present. Their number is variable but there is a gradual increase in their numbers throughout the stages I have studied. Thus, at 55 mm. only two were found; at 65 mm., eight; at 75 mm., seven; at 130 mm., thirty-eight; and at 171 mm., fifty-four. In older stages they were not counted but is it evident that they gradually become more numerous. However, age alone is not the sole factor which determines their number for in certain young specimens they were more numerous than in older ones.

The direction of the gland ducts is of interest for in nearly every case, just as soon as the duct leaves the urethral epithelium, it becomes directed bladderward, as described by Jarjavay (12) for the adult. In the connective tissue, however, their branches extend in all directions. Occasionally, however, gland ducts are found which are directed vertically to the urethral wall, or more rarely obliquely toward the glans penis.

That the glands of the urethra do not conform to a single type has been pointed out by a number of investigators, and various classifications of the urethral glands are to be found in the literature. Jarjavay (12) in 1850 attempted a classification, pointing out that the lacunae of Morgagni should not be considered as glands. Robin and Cadiat (23) described two types of

glands, one, the ordinary tubulo-alveolar gland, and the other, a follicular gland. The latter he subdivided into cylindrical sacs with but a single swelling at their bases, and those with bi- or tri-lobed bottoms. The latter type is described by Henle (10) as simple alveolar glands and by Delbert (5) as "glandes intramuqueuse." Herzog (11) classified the urethral glands as those belonging to the mucosa, evidently the follicular glands of Robin and Cadiat, and those belonging to the submucosa, including the tubulo-alveolar glands of Littre. Still another type of gland has been described in the cavernous urethra under the term "intraepithelial glands" by Klein and Groschuff (14), Branca (2), and Paschkis (21), the last-named author finding them constantly in true para-urethral ducts. Lichtenberg (16), in his study of the urethra divides the glands of the urethra into three types; first, sub-epithelial tubulo-alveolar glands, which are small in size and found equally distributed throughout the pars cavernosum; second, "gland-like pockets," irregular structures found only proximal to Cowper's ducts; and third, submucous tubulo-alveolar glands found only distal to Cowper's ducts.

From a study of the literature and from my own observations on fetal material, it is apparent to me that the glands of the urethra may present a variety of shapes. I have found the tubulo-alveolar (submucous) glands constantly in all specimens over 55 mm. In fetuses of 220 and 320 mm. and postnatal stages of two and one-half months and twenty months I have found varying numbers of sub- and intra-epithelial glands. In fetuses of 270 and 310 mm. none of the latter type of glands could be found. Simple alveolar glands are present in most of my specimens, but they are few in number. It seems to me, however, that any attempt to classify the glands of the urethra based upon their shape is more or less unsatisfactory. It is my belief that all types of glands found in the cavernous urethra represent developmentally and functionally identical glands in different stages of maturity; that the smaller and simpler forms are merely younger glands. In any stage, therefore, one may find all gradations of glands between the highly-developed, compound, tubulo-alveolar type and the simple intraepithelial glands.

The lacunae of Morgagni, which have created so much interest and discussion since their discovery might well be considered at this point. Almost without exception all investigators have placed them in a different category from the urethral glands. They differ from the glands in that they do not possess secretory cells, being lined with an epithelium similar to that of the urethra itself. Lichtenberg (16) has found them in the urethra of a child of two years, and Paschkis (20) writes:

> The statement of Debierres (cited from Zuckerkandl) that the lacunae of Morgagni appear postpartum, is not confirmed. I find quite typical, well-developed lacunae and mucous (Littre) glands in an embryo 30 cm. long.

Broman (4) in his figure of the urethra of a 13 cm. embryo has incorrectly labelled the urethral glands "lacunes of Morgagni." In my own specimens I have been able to find lacunae in one specimen only, that of twenty months, where they were few in number. I have searched in vain for them in my other specimens.

The lacuna magna, or sinus of Guerin, a blind pocket found on the pubic wall of the fossa navicularis, is still another inconstant structure of the embryonic male urethra. When present it courses parallel to the urethra, lying on its pubic wall, its ostium facing the external urinary orifice. It is lined with a stratified epithelium and possesses no secretory cell, neither do any gland ducts empty into it. The free edge at its ostium takes on in certain instances the form of a valve, as pointed out by Kusnitzky (15) and it is this structure which has received the name of "valve of Guerin."

According to the observations of Paschkis (21), a lacuna magna in the adult is usually present but its distance from the external urinary orifice, its length, its size and its anatomical form are extraordinarily variable. Van der Broeck (3) discusses its significance and concludes that it is not comparable to the true paraurethral ducts. He finds a similar structure in the urethra of certain marsupials.

In my own series I have found it present in embryos of 147, 220, 270 and 320 mm. but absent in all the others. Broman (4)

figures a wax reconstruction of the urethra of a 17 mm. embryo in which the lacuna magna is present.

Prepuce. The formation of the prepuce presents a problem which is of unusual interest. In the early embryonic stages the genital tubercle or phallus is covered by a layer of epithelium directly continuous with that of the anterior body wall. The distal end of the penis represents the glans, but there is however, no indication of a prepuce. In an embryo of 55 mm. the so-called glandar lamella has already made its appearance (fig. 1). This is an epithelial ingrowth from the epithelial covering of the

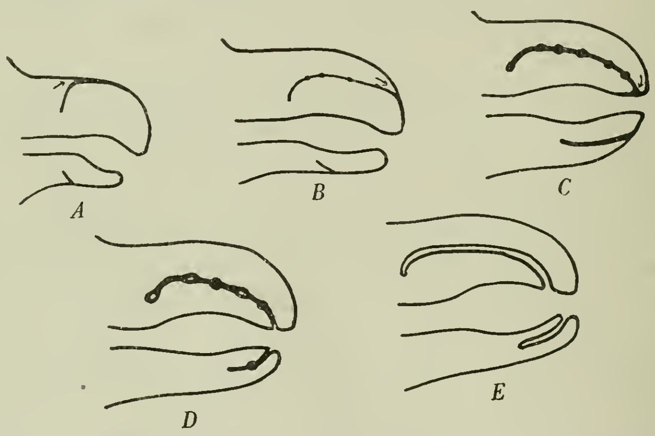


Fig. 12. Diagrammatic Drawings of Sagittal Sections of the Penis to Show the Development of the Prepuce

The prepuce has been drawn a little to one side of mid-sagittal, so as to show its ventral portion. This is absent in the mid-line, where the frenulum is formed.

phallus. It is situated near the middle of the phallus and is placed transversely. At 65 mm. it is more highly developed as shown in figure 13, a diagram of which is seen in *A*, figure 12. It forms an incomplete septum of the penis, the free edge being directed toward the urethral tube. Gradually the point of origin of the glandar lamella becomes shifted toward the end of the penis, so that its general direction when seen in sagittal section is no longer transverse, but longitudinal (fig. 12, *B*). The deep or free margin, however, does not change from its original position,

so that the glandar lamella becomes curved. This curve marks the corona of the glans. The shifting continues so that at 170 mm. (*C*) the attached margin of the glandar lamella is found at the external urinary orifice. The lamella becomes thickened, and epithelial pearls which have made their appearance, enlarge. In *D*, figure 12, a longitudinal splitting of the lamella is beginning at its attached margin, and the centers of the enlarged epithelial pearls are degenerating. At birth (*E*) or in postnatal stages, the splitting is completed and the epithelium of the glans and inner surface of the prepuce become completely separated.

With regard to the apparent shifting of the attached margin of the glandar lamella from the middle of the phallus to its distal end and eventually into the orifice of the urethra, the question arises by what means is it accomplished? Three methods of growth present themselves for consideration, namely; first, an actual shifting or sliding of the attached margin along the glans epithelium; second, an apparent shifting due to unequal growth and a gradual rolling in of the epithelium of the glans into the fossa navicularis; third, a constant splitting of the epithelium of the glans with the subsequent lengthening of the lamella as indicated by the arrows in figure 12. I have found it impossible to determine this point from a study of the sections, but I am inclined to favor the last described view as the most plausible.

REFERENCES

(1) Born, G.: Die Entwicklung der Ableitungswege des Urogenitalapparates und des Dammes bei den Säugetieren. Anat. Hefte, Ergebnisse, iii, 490–516. Wiesbaden, 1894.

(2) Branca, A.: Sur les glandes intra-epitheliales de l'urethre anterieur chez l'homme. C. R. de la Soc. d. Biol., lvi, 640–642. Paris, 1904.

(3) Broeck, Van der, A. J. P.: Über den Schliessungsvorgang und den Bau des Urogenitalkanales beim menschlichen Embryo. Anat. Anz., xxxvii, 106–120. Jena, 1910.

(4) Broman, I.: Normale und abnorme Entwicklung des Menschen. Wiesbaden, 1911.

(5) Delbert, P.: Urètre, in Poirier P. et Charpy A., Traité d'anatomie humane, v, 147. Paris, 1901.

(6) Eggerth, A. H.: On the anlage of the bulbo-urethral and major vestibular glands in the human embryo. Anat. Rec., ix, 191–206. Philadelphia, 1915.

(7) Ehrmann: Die Entstehung der paraurethralen Gänge. Wiener klinische Wochenschri ft. Wien., 1896.
(8) Felix, W.: The development of the urogenital organs. Keibel and Mall's Manual of Human Embryology, ii, 752–979. Philadelphia, 1912.
(9) Fleischmann, A.: Die Stilcharaktere am Urodaeum und Phallus. Morph. Jahrb., xxxvi, 1–26. Leipzig, 1907.
(10) Henle, J.: Handbuch der Systematische Anatomie als Menschen. Bd. II. Braunschweig, 1873.
(11) Herzog, F.: Beitrage zur Entwickelungsgeschichte und Histologie der männlichen Harnröhre. Arch. f. mikr. Anat. u. Entw., lxiii, 1904.
(12) Jarjavay, J. F.: Recherches anatomiques sur l'uretre de l'homme. Paris, 1856.
(13) Keibel, F.: Zur Entwickelungsgeschichte des Menschlichen Urogenital apparates. Arch. f. Anat. u. Entw., 55–156. Leipzig, 1896.
(14) Klein, G., and Groschuff, K.: Ueber intra-epitheliale Drüsen der Urethralschleimhaut. Anat. Anz., xii, 192–200. 1896.
(15) Kusnitsky: Untersuchungen über Richtung und Verlauf der Schleimhautfalten der ruhenden männlichen Urethra nach Plattenmodellen. Morph. Arb., viii, 65–94. 6. 1898.
(16) Lichtenberg, Alex.: Beträge zur Histologie, microskopischen Anatomie und Entwickelungsgeschichte des Urogenitalkanals des mannes und seiner Drüsen. Abschnitten I und II. Anat. Heft., xxxi, 65–196. Wiesbaden, 1906.
(17) Lowsley, Oswald S.: The development of the human prostate gland with reference to the development of the other structures at the neck of the urinary bladder. Am. Jour. Anat., xiii, 299–349. Philadelphia, 1912.
(18) Motz, B., et Batrina, J. M.: Contribution à l'étude des abcès perinéaux et des phlegmons diffus d'origine uréthrale. Ann. d. Maladies Organes Genito-urinaires, 1601–1630. Paris, 1903.
(19) Pallin, G.: Beitrag zur Anatomie und Embryologie der Prostata und der Samenblasen. Arch. f. Anat. und Entw., 135–176. Leipzig, 1901.
(20) Paschkis, R.: Zur Anatomie und Entwickelungsgeschichten der männlichen Harnröhre. Monatsb. f. Urol., xi, 641–662. Berlin, 1906.
(21) Paschkis, R.: Zur Kenntniss der accessorischen Gänge am Penis (Sogenannte paraurethrale Gänge). Arch. Dermat. Syphil., lx, 323–342. 1902.
(22) Pohlman, A. G.: The development of the cloaca in human embryos. Am. Jour. Anat., xii, 1–26. Philadelphia, 1911.
(23) Robin, Ch., and Cadiat: Sur la structure intime de la muqueuse et des glandes urethrales de l'homme et de la femme. Journ. de l'anat. et de la physiologie, p. 514–557. Paris, 1874.
(24) Rona, Peter: Die genese der paraurethralen Gänge mit besonderer Rücksicht auf die gonorrhoische Erkrankung derselben. Arch. Dermat. Syphil., xxxix, 27–50. 1897.
(25) Watson, E. M.: The development of the seminal vesicles in man. Am. Jour. Anat., xxiv, 395–441. Philadelphia, 1918.
(26) Wesson, M. B.: Anatomical, embryological and physiological studies of the trigone of the bladder. Jour. Urol., iv, p. 279–315. Baltimore, 1920.

ABBREVIATIONS USED IN FIGURES

Art., Artery
Bulb. ureth., Bulbus urethra
Circ. mus., Circular muscle of prostate
Corp. cav. p., Corpus cavernosum penis
Corp. cav. u., Corpus cavernosum urethrae
Cris. ureth., Crista urethralis (verumontanum)
Cyst. duct., Cystic duct
Duct. ejac., Ductus ejaculatorius
Duct. gl. b. u., Ductus glandular bulbus urethralis
Duct. meo., Mesonephric (Wolffian) duct
Ep. pearl, Epithelial pearl
Fos. nav., Fossa navicularis
Gang. sp., Ganglion spinale
Gang. symp., Ganglion sympatheticus
Gl., Glans penis
Gl. bul. ureth., Glandula bulbo-urethralis (Cowper's)
Gl. bul. ureth. acc., Glandula bulbo-urethralis accessoria
Gl. intrabulb., Intrabulbar portion of Cowper's gland
Gl. lam., Glandar lamella
Gl. ureth., Glandula urethralis
Isch., Ischium
Long. mus., Longitudinal muscle of prostate
Med. rap., Median raphe
M. bulb. cav., Musculus bulbo-cavernosus
M. isch. cav., Musculus ischio-cavernosus
M. lev. ani, Musculus levator ani
M. pyr. abd., Musculus pyramidalis abdominis
M. rect. abd., Musculus rectus abdominis
M. sph. ani ext., Musculus sphincter ani externus
M. sph. ani int., Musculus sphincter ani internus
M. sph. u., Musculus sphincter urethrae membranaceae
Or. ur. ext., Orificium urethrae externum
Pars amp. rect., Pars ampullaris recti
Pars anal. rect., Pars analis recti
Pars cav. u., Pars cavernosum urethrae
Pars memb. u., Pars membranacea urethrae
Pars pros. u., Pars prostatica urethrae
Per. cav., Peritoneal cavity
Prep., Prepuce
Pros. tub., Prostatic tubule
Rect., Rectum
Sym. p., Symphysis pubis
Ureth. pl., Urethral plate
Ut. vag. can., Utero-vaginal canal
Vag. masc., Vagina masculina
Vas. def., Vas deferens
Vert. coc., Vertebra coccygeus
Vert. sacr., Vertebra sacralis
Ves. urin., Vesica urinaria

PLATE 1

Fig. 13. Lateral view of a wax-reconstruction of the urethral epithelium of a human embryo of 65-mm. crown-rump length. $\times$ 33.

Fig. 14. Posterior view of same. $\times$ 33.

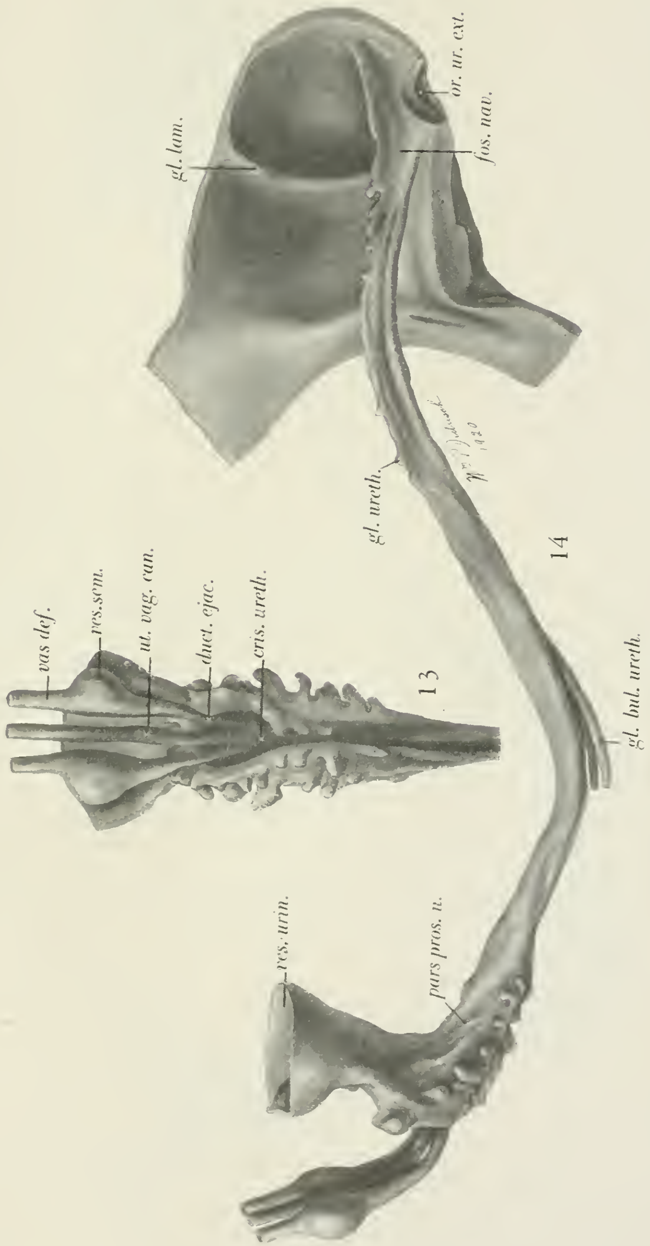
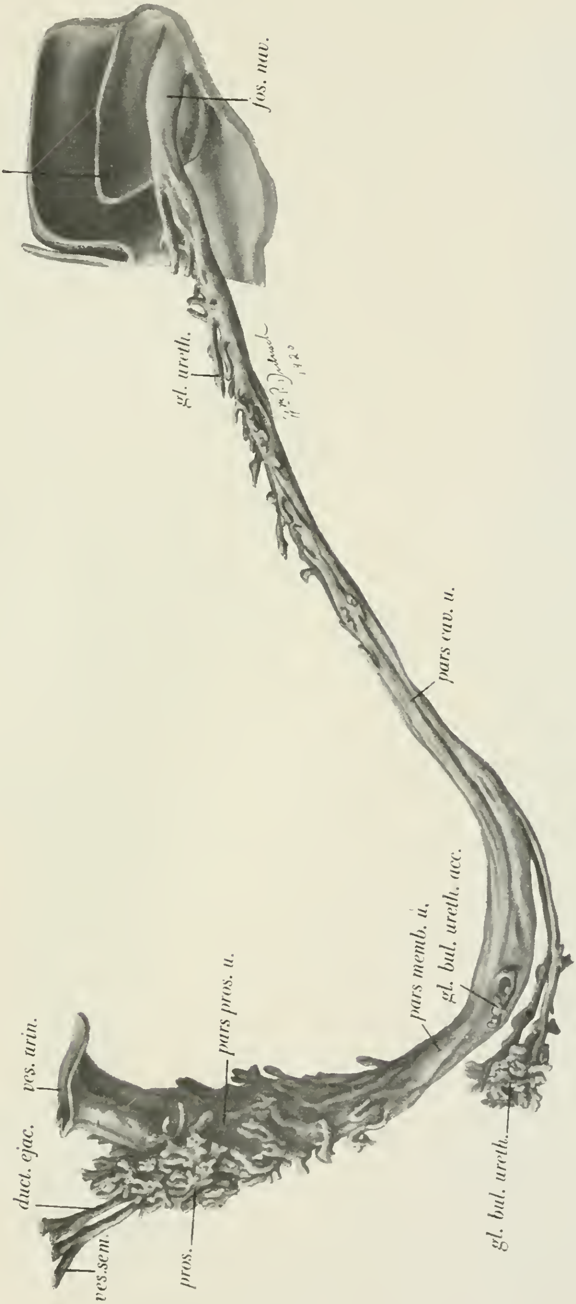

gl. lam.
or. ur. ext.
fos. nav.
gl. ureth.
14
gl. bul. ureth.
vas def.
ves.sem.
ut. vag. can.
duct. ejac.
cris. ureth.
13
ves. urin.
pars pros. u.

PLATE 2

Fig. 15. Lateral view of a wax-reconstruction of the urethral epithelium of a human embryo of 130-mm. crown-rump length. × 17.


gl. lam.
fos. nav.
gl. ureth.
pars cav. u.
pars memb. u.
gl. bul. ureth. acc.
pars pros. u.
ves. urin.
duct. ejac.
ves.sem.
pros.
gl. bul. ureth.

15

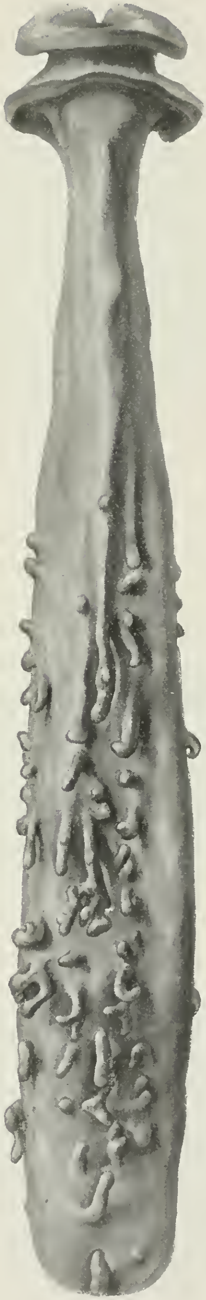
PLATE 3

FIG. 16. Posterior view of model shown in figure 15. × 33.

FIG. 17. Wax-reconstruction of the distal portion of the cavernous urethra of a human embryo of 171 mm. viewed from the pubic surface. × 17.


vas def.
ves. sem.
duct. ejac.
vag. musc.
cris. ureth.
gl. bul. ureth.
W. P. Didusch
1920

16

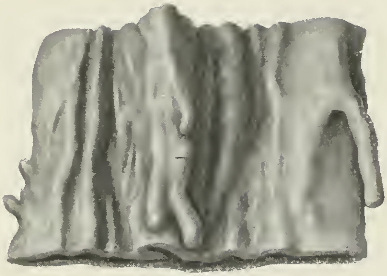


17

PLATE 4

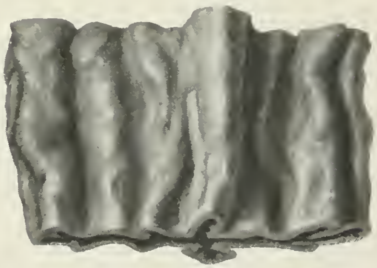
Figs. 18 to 23. Wax-reconstructions of various segments of the urethra of an embryo of 270 mm. All viewed from pubic surface. × 33.

18

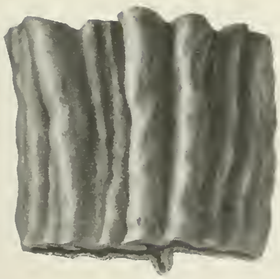


19

20



21



22

23

INTRACTABLE BLADDER SYMPTOMS DUE TO URETERITIS[1]

GUY L. HUNNER

From the Gynecological Department of the Johns Hopkins University and Hospital

The solution of the important problems relating to the so-called "Neuroses of the Bladder" still claims our attention and awaits further investigation.

The recognition that distressing bladder symptoms might torment the patient without the existence of a cystitis and because of a tuberculous lesion of the kidney and ureter was one of the comparatively early achievements of modern urology. We now know that either renal calculus or a chronic pyogenic infection of the kidney pelvis may likewise give rise to distressing bladder symptoms without local kidney pain and without evident lesion of the bladder mucosa. By recognizing these renal sources of bladder symptoms we take a large group of patients from the formerly obscure classification of "bladder neurosis," and by establishing a rational therapy we save a vast amount of suffering and of useless local treatment.

Modern urological methods have removed another large group from the "irritable bladder" classification by giving us a clear picture of the sequelae of acute gonorrheal infections. These often result in prolonged bladder distress because of the chronic trigonitis and chronic urethritis which may persist indefinitely if not properly treated.

My interest in the problem under discussion has led to previous reports on two groups of cases which we must have in mind in approaching this subject, and today I wish to propose that we remove a third group from that limbo of our ignorance commonly dubbed "bladder neurosis," in the hope that by giving to this

[1] Paper read before the Seventeenth Annual Meeting of the American Urological Association, New York City, March 25, 1920.

group a definite pathological classification we may be able to work out a rational and effective line of treatment.

In December, 1910, I reported before the Southern Surgical and Gynecological meeting at Nashville, on "Chronic Urethritis and Chronic Ureteritis Due to Tonsillitis"[2] and proposed the theory that many of our cases of chronic urethritis formerly classified as rheumatic or as gonorrheal urethritis really belong to a group of cases due to focal infections. I reported cases of the most extreme bladder distress apparently due to a chronic urethritis which refused to improve materially under the usual methods of treatment but which recovered promptly and permanently after removal of the tonsils.

Since that time I have had many similar cases clear up after the removal of tonsils, drainage of sinuses, or extraction of abscessed teeth, and I have had the satisfaction of having colleagues over the country tell me of similar experiences.

At a meeting of the New England Branch of the American Urological Association in December, 1914, I read a paper on "A Rare Type of Bladder Ulcer in Women."[3] I reported eight cases of this type of cystitis which we had formerly overlooked and had classified as "bladder neurosis" or as chronic urethritis, because of the frequent association of this lesion.

I have now seen about forty-five of these cases, and cases have been reported by C. A. L. Reed of Cincinnati.[4] Dr. Floyd Keene of Philadelphia, associated with John G. Clark, recently reported ten cases of this disease and his paper is soon to appear in the Annals of Surgery. H. A. Fowler of Washington is to report three cases of this type at the New Orleans meeting of the American Medical Association. In discussing the possible etiology of this type of bladder ulcer in my first paper on the subject I emphasized the fact that none of the usual causes of cystitis could be traced in the onset history of these cases.

I classified this lesion as "simple ulcer" because the accepted meaning of such lesion in the bladder is an ulcer arising from an

[2] Jour. Amer. Med. Assn., 1911, lvi, 937.

[3] Boston Med. and Surg. Jour., 1915, clxxii, 660; and Trans. Southern Surg. and Gynecol. Assoc., 1914, xxvii.

[4] Jour. of the Amer. Med. Assn., Feb., 1918, lxii, 332..

embolus or thrombosis, presumably from some distant focus of infection. I emphasized the lack of apparent local etiological factors and the existence of urine sterile to our usual methods of culture. The conclusion in that first paper on this type of bladder ulcer was that "the histories and examinations of these patients have not borne out the theory of a distant focus of infection in the striking manner we find to be the rule in most ureteral stricture cases."

Further experience with these cases, however, and more careful history taking and more minute attention to possible foci of infection has led me to reverse that opinion.

One of the most striking circumstances leading to this reversal of opinion is the recent discovery that many patients suffering with this type of bladder ulcer have at the same time, or subsequently develop, ureteral stricture. In one of my resection of the bladder cases the patient came back later, suffering with symptoms due to ureteral stricture. In three of my bladder ulcer cases pyelitis developed during convalescence from the bladder operation and all three women were found to have ureteral stricture. Of the last twenty patients with an elusive ulcer studied since my last report, only eight of them operated on as yet, seven have had symptoms leading to the investigation for and the discovery of ureteral stricture. We can no longer make the finding of a sterile urine one of the criteria in diagnosing a case as elusive ulcer, because the patient may possess ureteral stricture and a pyelitis (usually a colon infection) secondary to the stricture with its urinary stasis. The presence of the bladder ulcer and the wide-spread thickening of the bladder wall might be expected to interfere with the normal evacuation of the urine, and lead readily to a secondary infection due to the multiple investigations and treatments which so many of these patients undergo, but they have been found strikingly free from infection unless associated with ureteral stricture and secondary kidney infection.

My experience with ureteral stricture cases leaves no room for doubt as to the focal infection theory answering for the etiology in the vast majority of these cases.

I think we may now state with full confidence that time will demonstrate the truth of our contention that most of the obscure

cases we have formerly diagnosed as "bladder neurosis" fall into one of three groups. We have (1), the cases of chronic urethritis with or without trigonitis; (2), the elusive ulcer group in which the apparent tiny ulcer or ulcers on the surface of the mucosa usually form an insignificant part of the total lesion, which consists of a wide-spread chronic infiltration of all coats of the bladder wall; (3), we have the group under discussion today in which the chronic infiltration of the walls of the lower ureter results in the lesions characteristic of ureteral stricture, and often causes symptoms chiefly referable to the bladder. If our theory is correct that focal infections are the cause of these lesions in the majority of cases, we can make the further important statement that the successful treatment of these cases demands the finding and removal of a distant focus of infection.

URETERITIS AS THE CAUSE OF INTRACTABLE BLADDER SYMPTOMS

On giving the matter consideration it is surprising that we have not earlier sought for a ureteral lesion to explain some of our obscure cases which until now we have been classifying as bladder neurosis because of the absence of a visible bladder lesion.

We are familiar with the bladder distress associated with the tuberculous kidney, and often occurring in such cases without any visible bladder lesion, or at most with a slight reddening and edema about one ureteral orifice. In such cases we can usually find palpable thickening of the lower end of the ureter, and pressure on this thickened ureter causes the intense bladder distress. It is probably the ureteral rather than the kidney lesion which gives rise to the urgent micturition impulses in such cases.

Similarly in the infected calculus kidney cases and pyogenic pyelitis cases we can usually make out on palpation a slight thickening and elicit great tenderness of the lower portion of the ureter, and peristalsis of the tender ureter is probably an important factor in the reflected bladder distress.

I have shown in a previous publication[5] that many ureteral calculi are secondary to a local inflammatory area in the ureter,

[5] The Etiology of Ureteral Calculus. Surg., Gyn. and Obst., 1918, xxvii, 252.

and it is only reasonable to conclude that such an area, whether containing a stone or not, is likely to set up nerve impulses referred to the bladder.

I regret that I have not had the time for the tabulation of all my ureteral stricture cases to find how many of these patients have complained of bladder symptoms. In my last one hundred cases diagnosed as ureteral stricture, occurring between June 1 and December 1, 1919, in seventy-one there were bladder symptoms. In thirty-three of these the bladder symptoms were a marked and more or less constant feature of their complaint, and in the thirty-eight classified as having mild bladder symptoms, many had rather severe bladder symptoms during their attacks of renal pain due to partial or complete closure of the stricture area.

ETIOLOGY AND PATHOLOGY

My views on the etiology and pathology of ureteral stricture or of simple chronic ureteritis have been presented in previous publications and have been referred to above, but it may be well to elaborate them here because of the relationship in the particular class of cases under discussion to conditions in the trigonum and urethra.

In my original communication on chronic urethritis and chronic ureteritis caused by tonsillitis emphasis was placed on the tonsils as the primary focus of infection. A further study of about eight hundred cases has taught that in children the tonsils supply the focus in the vast majority of cases, while a few depend on sinus infection. In cases coming on in early adult life the tonsils probably still lead in etiology, while in later adult life the teeth are more often responsible. The sinuses seem to be the starting point in many adult cases and a few are probably due to the intestinal tract. While I do not find much evidence that the intestinal tract plays an important rôle in the causation of the stricture, I do think that the infection of the static urine secondary to the ureteral narrowing not infrequently follows inflammatory conditions in the bowels.

If we are treating a case of ureteral stricture in which a secondary pyelitis has developed we shall find the occasional case

in which strict attention to the diet and gastro-intestinal functions are a sine qua non of success.

We find, however, that there are many more patients who are suffering with gastro-intestinal symptoms secondary to the ureteral and kidney complications, and that with the relief of the urinary tract lesions these bowel conditions clear up without special attention to the digestive tract.

From the fact that most ureteral strictures are found in the broad ligament region and that the second most frequent site of narrowing is in the region of the iliac glands, I believe that the original infection or toxin may be first arrested by the lymph glands in these regions and that the inflammation then settles in the ureteral walls and causes inflammation, infiltration, and narrowing of the lumen.

Without exact tabulation of my records I have previously estimated that at least two-thirds of the patients with ureteral stricture have infiltration of the urethra as well. On careful analysis of the last one hundred stricture cases above referred to, I was surprised to find eighty-five cases were classified as having infiltration of the urethra. In some of these the shrinkage and obstruction to the urethral dilator was undoubtedly due to senile changes, in some to past gonorrhea, or to other infections of the urethra coming from the exterior. At times this infiltration is found to be a general thickening and narrowing of the entire urethra and at times one or more annular strictures are found, most often about the inner third of the urethra. Many cases thus found with urethral stricture have no bladder symptoms and the urethral mucosa may or may not show a granular reddened condition. In other words we find cases with infiltration of the walls of the urethra without apparent signs or symptoms of mucosa involvement and in some cases even with the mucosa involvement, there is absence of bladder symptoms.

We also find in many cases of ureteritis an involvement of the trigonum. The mucosa of the trigonum may be slightly congested, and somewhat tender on pressure and in such cases the patient may never have complained of bladder symptoms. The trigonum may be edematous and angry red or it may show a

massive edema with a greyish color or there may be the condition commonly described as bullous edema in which a dark red background is covered with vesicles or large bullae. Elevated areas of dead white mucosa, the so-called leukoplakia vesicae, are not extremely rare.

Most of the patients with marked trigonal involvement complain of bladder symptoms, but we wish to emphasize in this paper that we have some patients suffering from ureteritis who complain of marked bladder symptoms, and who have no apparent involvement of the trigonum or urethra; and furthermore, if they show trigonal and urethral inflammation, we may get at least temporary clearing up of these conditions without material improvement in the symptoms, because these are due chiefly to the ureteritis.

We thus see that we may have involvement of local areas of the ureteral walls, and that in over two-thirds of these cases there is involvement of the deep tissues of the urethra, and it is probable that in most of such cases the tissues of the bladder base are also inflamed, although this may not show on the trigonal surface. Why the purely ureteral case is often associated with bladder symptoms, rectal pressure, vaginal wall pain, pains referred to the outer perineum, etc., is more easily explained on the hypothesis of referred pain, than is the fact of evident involvement in other cases of the trigonal and urethral walls without complaint of bladder symptoms.

SYMPTOMS AND DIAGNOSIS

The bladder symptoms due to ureteritis are at times those characteristic of a cystitis and the diagnosis can be made only by a careful examination of the ureter. But as a matter of fact this is usually done only after exclusion of the other possibilities. More often there are in addition to the bladder disturbances certain symptoms which lead one to suspect ureteral stricture from the history alone, and if the palpation findings verify the suspicious history, one is practically certain of the diagnosis without further examination.

The diagnosis of simple, inflammatory ureteritis as the cause of intractable bladder symptoms will usually have to be made between this condition and four other disease entities; two of them, tuberculosis of the kidney and ureter, and elusive ulcer of the bladder, being comparatively rare, and two of them, chronic urethritis and trigonitis of gonorrheal origin, and the same condition of focal infection origin, being comparatively common.

A sudden onset of bladder symptoms coming "out of a clear sky" with no previous history of recent operation, childbirth, abortion, gonorrheal infection, or other event usually concerned in the onset of cystitis, always makes one think first of tuberculosis of the urinary tract. As in tuberculosis the patient with simple chronic ureteritis may have had a sudden onset with the bladder distress and these symptoms may have persisted for years, but it is usually easy to differentiate between the two diseases by our anamnesis and early examinations.

In the tuberculosis case we may find evidence of this disease elsewhere in the system which is at least suggestive. In the ureteral case we may have a history of sinusitis, tonsillitis, abscessed teeth, or gastro-intestinal trouble, or careful examination will show evidences of focal infection in these areas. The sudden onset of bladder symptoms may have followed an acute exacerbation of trouble in one of these areas, or it may have followed one of the acute infectious fevers such as scarlet fever, measles, and particularly influenza.

Palpation findings are similar in the two diseases, i.e., the patient is likely to show tenderness in one or both kidney regions, in one or both ureteral regions at the pelvic brim, and especially in the broad ligament region, where the affected ureter may be felt enlarged and tender. The tuberculosis case is more likely to show unilateral involvement. Simple ureteritis is bilateral in more than one-half of the cases. The tuberculous ureter is often very thick and feels nodular. The ureter with simple inflammatory involvement may not be thickened enough to be certainly outlined by palpation, or it may have a wire-like thickening over a diffuse area, or it may present a local nodular area of stony induration.

The urine after a long history of bladder symptoms will show in the tuberculosis case a large amount of pus. Here we must except the extremely rare case of tuberculous kidney which has become "dead" and in which the bladder urine may be almost if not quite normal.

In the ureteritis case the urine may be absolutely normal or it may contain a trace of albumin, or show a few erythrocytes or leukocytes, or both, or if a secondary pyelitis has developed the urine will show the picture characteristic of this latter condition. Many of the so-called idiopathic hematuria cases, with or without pain symptoms, are associated with ureteral stricture. The bladder urine culture on slant agar in either disease is negative unless a secondary invader, usually the colon bacillus, has settled in the bladder or kidney. Tubercle bacilli should be found in eighty per cent. of the cases of these urinary tract infections.

One of the most suggestive points in getting the history of a patient suffering with bladder symptoms due to lesions secondary to focal infections is the intermittency of the symptoms. In the majority of real cystitis cases as well as in most cases of tuberculosis of the kidney and ureter associated with bladder symptoms the patients complain of more or less constant symptoms day and night. This rule holds with the elusive ulcer cases, and in fact these patients suffer more than most other chronic bladder victims unless it be those with badly contracted bladders secondary to tuberculosis of the kidney. One might argue that if these elusive ulcer cases are due to focal infections they should also show the intermittency of symptoms, but it is probable that the presence of an open ulcer in these cases is the chief factor in the constant misery rather than the wide-spread infiltration of the bladder walls. By the destruction of the terminal nerve filaments in the ulcer area with an application of the actual cautery wire, the pure silver stick, or even the topical application of 10 per cent silver solution, these patients will often go for six or eight weeks in comparative freedom from their agonizing symptoms.

The symptoms in the ureteral stricture cases as well as in the cases of trigonitis and urethritis may be as constant and as severe

as in any other form of bladder trouble, but if we find a patient with intermittent bladder symptoms, we must at once suspect these focal infection lesions.

The intermittency is variable. One patient has all her bladder distress at night, being quite free of symptoms in the day. Another patient is troubled only in the daytime, and many of the ureteral stricture patients have most of their discomfort early in the morning. The tissues in the broad ligament region seem to become stiffened during the night's rest, and the patient complains of being awakened early in the morning with considerable pelvic pain and an intense desire to void; indeed, the soreness and pain on the first few voidings may be so severe that the act becomes almost impossible. After an hour or two of frequent and painful voiding and after becoming active with the duties of the day the tissues in the ureteral region seem to lose their soreness and the patient becomes more comfortable.

The intermittency may extend over a period of days, weeks or months and the patient may have complete cessation of symptoms or only comparative comfort during these intervals.

Most cases with bladder symptoms due to chronic urethritis and trigonitis are characterized by a negative urinalysis, or at most there may be an occasional leukocyte in the urine, and there may be an excess of epithelial cells due to the rapid exfoliation of the inflamed trigonal area. If the condition has progressed to actual loss of surface epithelium or to ulcer formation on the trigonum, the urine may contain more or less blood.

The cases of urethritis and trigonitis due to gonorrheal infection are differentiated by the history, the appearances of the external genitalia, the cystoscopic findings, and the reaction to treatment.

The history in the gonorrheal case usually includes a sudden, acute onset of intense bladder symptoms synchronous with or following shortly after the onset of an acute and profuse leukorrhea. The bladder and urethral symptoms may have been so severe at first that the patient was afraid to void because of the pain, or the urethra may have become so edematous that the patient could not void and had to be catheterized. In this

stage there is likely to be much pus and some blood in the urine. With or without treatment such an acute onset has probably been followed in from four to eight weeks by such an improvement that the patient considered she was getting well, and she may have failed to consult a physician. If under treatment up to this improvement stage, she felt justified in ceasing further treatment, only to be disappointed in having a modicum of her symptoms persist, usually as a burning uneasy feeling in the bladder with frequency and burning or scalding on voiding.

After a few or many months of this chronic stage she again takes up treatment by the family physician, getting medicines by mouth or possibly bladder irrigations with such disappointing results that she is finally referred to the urologist. His investigations elicit the above typical history, evidences of a past gonorrheal infection about the crypts and glands of the external urethra and the vulva, and a cervicitis with its leukorrhea. On cystoscopy the urethra is found to be sensitive and probably infiltrated and contracted. The bladder is normal except for the trigonal region. The ureteral orifices are likely to be altered from the slit-like openings to small round or even pin-point openings, with pale white scarred edges. Immediately about the openings, there may be brilliant red groups of minute vessels, or the regions around them may have about the normal supply of vessels except on the median or trigonal side of the orifice where there is a brilliant red spot from 1 to 3 mm. in diameter, which at first appears like a petechial submucous hemorrhage, but which on careful inspection is found to be composed of a group of tiny vessels.

The treatment of such a case is usually most satisfactory. Thorough dilatation of the urethra with swabbing of the trigonum with a 10 per cent solution of silver nitrate and of the urethra with a 3 per cent silver solution will usually result in prompt and permanent relief. If the deep suburethral or Skene's glands still harbor a gonorrheal infection, they may have to be opened and destroyed before the urethral catarrh can be controlled.

The cases of chronic urethritis and trigonitis due to focal infections may present the same cystoscopic picture as the chronic gonorrheal cases, but they usually differ in the history, in the

findings about the external genitalia, and in their reaction to treatment.

The onset may have been sudden and acute, but it is rarely of such intensity as in the gonorrheal case, the patient merely complaining of a greater frequency and of burning on voiding. After a brief attack the patient may recover for a shorter or longer period and then have another similar attack. The attacks may increase in frequency, in severity, and in duration, and may settle into a chronic condition. The intermittency is a most suggestive feature in all focal infections as was mentioned above in the discussion of the cases due to ureteritis, and treatment of the trigonitis and urethritis by the method above described for gonorrheal cases may result in as prompt and satisfactory results as in the gonorrheal case. If the original focus of infection persists these cases may show very little or no improvement from the local treatment; or, if they apparently clear up under treatment, they are certain to return with their original symptoms whenever the focal infection again becomes active.

The focal infection cases rarely show the evidences of inflammation about the external genitalia, but one sees an occasional case with vulvitis, cervicitis, and the brilliant redness about the mouths of the paraurethral glands exactly as in the gonorrheal cases in patients in whom a past gonorrhea can be ruled out with practical certainty.

We spoke of the ease with which most gonorrheal cases can be relieved, but one finds an occasional case in which a past gonorrhea is a positive factor, and which is most obstinate in answering to treatment. In such a case we must not forget that gonorrhea and focal infections are both of common occurrence and may both need consideration in the treatment of any obstinate case.

In previous publications, referred to above, also "A Rare Type of Bladder Ulcer. Further Notes with a Report of Eighteen cases"[6] and "Elusive Ulcer of the Bladder, Further Notes on a Rare Type of Bladder Ulcer, with a Report of Twenty-five Cases"[7] on the elusive ulcer of the bladder I have emphasized the protean

[6] Jour. Amer. Med. Assoc., January, 1918, lxx, 203.

[7] Amer. Jour. Obstet., 1918, lxxviii, no. 3.

character of the referred pains suffered by these patients which have led to all manner of useless pelvic and perineal operations in the attempt to alleviate the patient's symptoms. In my publications on ureteral stricture[8] I have emphasized the same multiplicity of symptoms in this disease which have led to errors in treatment, and are continuing to subject every year literally thousands of patients to fruitless operations on the abdominal and pelvic organs because of the lack of a correct diagnosis.

Further details of the unusual and even weird symptoms obtained in some of these ureteral stricture cases will be left for the subjoined case records, where they may be studied by those sufficiently interested in the subject.

My treatment of ureteral stricture has been sufficiently explained in previous publications, and the method of handling patients suffering with persistent bladder symptoms can be learned by a study of the case records. It may be well to emphasize again that the beginner in ureteral stricture work is likely to overdo in the matter of investigation and treatment. A strictured ureter should not be dilated oftener than once in ten days. In the densely infiltrated cases where it is difficult to get through it is better to allow a full two weeks for the subsidence of the edema and inflammation incident to the trauma of treatment, before again attempting to dilate.

In bilateral stricture both sides should never be investigated or dilated at the same sitting, and it is safer to have an interval of three or four days between the treatments of the separate sides, because the first side treated may not develop sufficient edema to entirely shut off the kidney until after forty-eight hours. In suspected bilateral stricture thorium X-rays should never be made of both sides at the same sitting for the reaction is often much more severe after the use of thorium than after the simple dilation treatment.

Case 1. Miss B. M., aged twenty-five years, first consulted me on September 9, 1914, complaining of bladder trouble of six or seven

[8] Ibid. also Ureteral Stricture, Report of 100 Cases, Johns Hopkins Hospital Bulletin, 1918, xxix, no. 323; and Differential Diagnosis in Stricture and Calculus of the Ureter, N. Y. State Jour. Med., September, 1919, xix, no. 9, p. 323.

years' duration. There is more or less constant desire to void in the day and she is up eight or ten times at night. She is always worse in cold weather. At times she is fairly comfortable for days at a time.

Two years ago the patient was found to have a lung lesion in the right upper lobe and after a few weeks at the State Sanatorium she has lived an out-door life and has no trouble from this now. Two years ago she had treatment in a hospital for the bladder trouble without special improvement.

On finding a normal urine and nothing to account for the bladder symptoms except a mild reddening of the trigonum and urethra, I inquired about possible foci of infection, and found that the tonsils had been removed two years previously. For three or four years she has had headaches most of the time in the temporal and occipital regions, exaggerated at the menstrual periods, and not influenced by wearing glasses.

Her menstrual periods began at fourteen years of age, and were always approximately regular, lasting for three days, and associated with backache, increased pains about the bladder, and cramps in the uterus. The uterus was found in extreme retroposition and flexion.

After four treatments for the mild trigonitis and urethritis the mucosa appeared normal and the bladder symptoms were considerably improved.

Because of her menstrual symptoms and the extreme retroflexion I operated on September 24, 1914, doing a thorough dilatation of the cervix and a round ligament suspension of the uterus. The appendix was found to be quite long and its outer surface was covered with dilated vessels. There were a number of light adhesions about the ileo-cecal valve region and I made a note at the operation that these evidences of chronic appendicitis might explain the patient's bladder symptoms for which we had not found sufficient cause.

The patient gained in weight and had better general health after the operation but her bladder symptoms continued about the same.

About one year later, in November, 1915, I sent the patient to Dr. J. J. Bordley because of her continued headaches. He found some badly infected roots of tonsils and removed these. Within six months after the removal of the tonsil stumps and without further treatments of the trigonum and urethra her bladder symptoms of seven or eight years' duration got distinctly better.

In April, eighteen months after the tonsil removal, she reported "If I take cold it settles in the bladder—otherwise I have but little trouble."

Soon after the uterine operation the patient complained of a dull pain in the lower right abdomen near Poupart's ligament, which we interpreted as probably due to the suspension of the round ligament in this region.

Five years after the operation, or in August, 1919, the patient returned complaining of this same pain with a similar pain in the left lower quadrant and pain at times in both kidney regions.

These symptoms, together with the past history of bladder trouble and the trigonitis and urethritis which improved only temporarily under local treatments and made distinctly greater improvement after tonsillectomy made me think at once of ureteral stricture. She was found to have a reddened trigonum and urethra, and bilateral ureteral stricture. Three treatments on each side exaggerated her old symptoms of local pain in the broad ligament regions, pain in the kidney and the old bladder distress, but the patient steadily improved during her two months of treatments and she has not been heard of since going home.

Case 2. Mrs. J. C. S., aged forty-eight, referred on March 4, 1915, by Dr. Grubb of Berkeley Springs, W. Va. One child fifteen years ago, delivered with instruments. Repair at time of delivery and repair one year later.

The patient complained chiefly of bladder distress and of a pain and soreness through the lower abdomen which came intermittently and at times lasted several days. At times there were paroxysms of pain in the left side of the vagina which could be partially relieved with hot douches. This pain was exaggerated after stools. There was often incontinence of urine.

This patient was seen a few months before my special interest in ureteral stricture had begun. She had been seen by a gynecologist one year previously and had been advised an operation for her cystocele. She was brought by her family physician to the Union Protestant Infirmary and I was requested to operate the next day before the physician returned home.

A Wertheim interposition operation was done the following day with puckering of the urethral region with four black silk sutures. The only benefit the patient derived from this operation was an improvement in her incontinence. All of her old abdominal, bladder, and vaginal distress persisted and she occasionally had slight incontinence.

With our present knowledge of such cases this patient would not have been submitted to operation, and it is likely that with the improve-

ment of her ureteral and trigonal conditions the occasional incontinence would have been greatly benefited without the operation for puckering of the urethra.

At my preliminary history-taking and examination I found that the patient had had throat and nose symptoms and much earache the previous year, and that she had had tonsillitis off and on for about sixteen years.

The trigonum was red and granular looking and the base of the bladder showed considerable increase in redness. The catheterized bladder urine showed a few leucocytes, many rod bacilli, some in large clumps, and a trace of albumin. There was no note made at the time concerning the palpation of the ureteral regions and the only pathological condition noted was the moderate relaxation of the outlet and the presence of a moderate cystocele.

The patient returned in May, 1916, complaining of all of her former symptoms. Her bladder trouble was chiefly in the latter half of the night. She usually slept until about 4 a.m. when she was awakened with pain, chiefly in the left side of the vagina and an intense desire to void. She usually got no more sleep because of the frequent voiding until it was time to get up.

Examination showed extreme tenderness over the base of the bladder and the lower ends of both ureters. Palpation of the broad ligament portion of the left ureter caused her to cry out with pain. Investigation revealed stricture of both ureters with bilateral pyelitis. In the intervening four years the patient has visited the hospital once or twice a year for ureteral treatments and pelvic lavage. Her tonsils have been removed and a few abscessed teeth extracted. She has gradually improved. She was last seen in February, 1920, when her general health was found considerably improved, her old paroxysms of pain in the left vagina had almost entirely disappeared, and her bladder distress was negligible except for occasional mild attacks. She had recently been visiting in Washington and while there had an attack of pain in the upper right quadrant with a temperature of 100° which was thought to be due to "liver trouble" or influenza.

Examination revealed much less redness about the base of the bladder and trigonum than in her early treatments. There were still a few leukocytes and a trace of albumin in the catheterized bladder urine. The strictures were dilated with 4.6 mm. bulbs and the hang of the bulb on either side awakened the old bladder distress while the left bulb caused the old paroxysms of pain in the left side of the vagina.

While her urine was free from organisms on her last previous visit, one year before, the right kidney now yielded a culture although there were no leukocytes. It is probable that her attack two weeks previously with slight fever and a pain in the upper right quadrant had been due to a low grade pyelitis.

Case 3. Mrs. E. L., aged forty-three years, referred by Dr. A. D. Heller of Bethlehem, Pa. The patient had complained of bladder trouble for the past twelve years. On taking her seat in the office she said, "Doctor, I do not know that I have a bladder in the daytime but the minute I hit the bed at night the bladder begins and gives me Hell all night." On her best nights she was up only two or three times and on her bad nights six or eight times. She said there was no acute pain but a constant dull pain like a toothache until the bladder was emptied. If the bladder was full she was tender on pressure in the hypogastric region. After an almost sleepless night she would drink several cups of black coffee for breakfast and be entirely free from bladder discomfort during the day. There had been much intestinal trouble in the form of flatulency and diarrhea. There is often a heavy pressure in the lower part of the rectum during the night. Dyspareunia is complained of.

There has been much pain in the lower right side and down the right thigh. Ten years ago Dr. Noble of Philadelphia did a fixation of her right kidney without improvement in her symptoms, and four year ago Dr. Deaver removed her appendix and suspended the uterus, when it was prophesied that her attacks of diarrhea would cease.

Cystoscopy showed an infiltration of the urethra, the bladder mucosa appeared to be normal, the trigonum was considerably reddened and covered with a few opalescent vesicles. Both ureteral orifices were puffy, red, edematous looking. The urethral mucous membrane showed the normal red and white striae. The urine showed a few leukocytes and a few erythrocytes but no albumin. A culture from the bladder grew colon bacilli as did later cultures from both kidneys.

The first attempt to dilate each ureter was a failure because of the dense infiltration in the lower ends. On the second attempt on either side a whalebone filiform was first introduced as a guide when the renal catheter with the wax bulb was passed along the filiform and up to the kidney. Both ureters had strictures in the broad ligament region 3 cm. above the bladder. The right kidney held over 1 ounce and the left kidney about 13 cc.

The patient was kept in the hospital during March and April, 1919, having four dilatations on each side together with lavage of the kidney pelves with 1: 1000 silver nitrate solution. After each of her early treatments she was much disturbed with the flatulency and diarrhea for from one to three days, but before she returned home these symptoms had ceased even after the treatments. The colon bacillus culture had become negative. She frequently slept through the night without voiding but occasionally she voided once or twice during the night, after excessive water drinking. The pain in the lower right side, in the hip, and down the thigh, exaggerated by each right side treatment, had ceased.

The patient went to Atlantic City for the summer and on resuming her habitual indiscretions in diet she was soon having her old bladder distress at night. On December 8, 1919, an examination of the bladder urine showed that a culture was again present and there were a few leukocytes and a few erythrocytes.

Cystoscopy showed about the same picture as formerly. There was some general reddening of the trigonum but the appearance about each ureteral orifice was far less inflammatory looking, there being a small red papilla to the median side of each orifice instead of the general red, bullous edema present at the first examination. The ureters were not examined, as the patient was just then beginning intestinal treatment with Dr. LaBarre of Allentown, Pa. One month later the patient came for examination and reported that the bladder trouble had ceased. She was not getting up at night and could hold the urine indefinitely in the daytime and she had lost the sensitiveness in the bladder region. There was still an occasional leukocyte and erythrocyte in the urine but the culture taken from the bladder was sterile.

Case 4. Mrs. J. F. N., aged sixty-four years—8 para, oldest forty five years, youngest thirty-three.

For the past three years the patient has been in the hands of some of the best medical men in the city being treated for rather vague and indefinite symptoms of numbness and giddiness and for a pain in the lower right quadrant and intermittent bladder symptoms.

The bladder symptoms consisted merely of a frequency which for two years had been awakening her at four or five o'clock in the morning and compelling her to get up from two to four times between the first voiding and the hour of seven, when she arose for the day. During this two or three hours of the early morning there was considerable pain and she was compelled to lie on the right side. After getting up

for the day she became more comfortable and held the urine for three or four hours. She slept well at night without arising until the early morning hour.

About one year ago she had a sharp attack of pain in the right back for which her daughter, a nurse, used a flannel cloth and hot flatiron. For the past month she has been having considerable pain in the upper right back.

She was examined by Dr. E. H. Richardson three or four months ago and a large round ring pessary was placed without altering her symptoms.

Examination. The patient is a large florid woman in apparently good health. She has never had tonsil or throat trouble but the tonsils are rather large for one of her age. The upper teeth are false, the lower back teeth are absent and the six front lower teeth show much pyorrhea. Heart normal. The patient points to her pain as being deep, back of the right Poupart's ligament.

Neither kidney could be palpated and there was no tenderness in the upper right flank. Palpation of the broad ligament regions through the vagina—no tenderness over the left ureter, very tender over the right ureter and the patient says this reminds her of the old pain and causes her desire to void.

The urine showed an occasional leukocyte, a few erythrocytes and a trace of albumin.

Cystoscopy. The urethra easily dilated to 10 mm. The bladder was normal. The trigonum was somewhat reddened, the patient having a distinct cystocele. The right ureteral orifice region appeared normal.

A 4.5 mm. wax bulb obstructed fairly definitely going in and gave definite hang on withdrawal. The kidney content was about 15 cc. There were three areas of infiltration in the ureter, one at 9.5 cm. from the outside and two other areas nearer the bladder.

The patient had six dilatations from November 15, 1918 until April 28, 1919, the last wax bulb used being 5.6 mm. in diameter. She improved from the very first treatment and after the second treatment she was so much improved, she insisted on having the pessary removed, saying that it had not influenced her symptoms.

A letter from this patient on February 11, 1920 says, "I am pleased to report my general condition good. I do not have any of my old bladder symptoms and the numbness from which I formerly suffered has entirely left me."

Case 5. Miss S., aged forty-seven, referred by Dr. W. W. Russell on December 31, 1919. For ten years the patient had had a varied history of operations, rest-cures, and work-cures.

She was first admitted to the Union Protestant Infirmary in April, 1909, and gave the history that she had always been in excellent health up to one year previously, when she had a severe attack of nervous prostration. During that year she had developed profuse menstruation with severe headache. About a month before admission she had an attack of pain on the right side and she was admitted to the hospital because of a second similar attack. Dr. Finney and Dr. Russell operated, removing a supposedly chronic appendix, dilating and curetting and suspending the uterus. The urine on this admission showed a trace of albumin.

Three years later or in January, 1912, the patient was again admitted to the hospital and operated upon by the same surgeons, the pelvic organs being removed by supravaginal hysterectomy, the diagnosis being "adeno-myoma of the uterus." The patient had done fairly well for about two years after her first operation, but had some obscure abdominal pain and much nervousness.

In February, 1911, she had a bad fall, and from that time on she had abdominal pain practically all of the time except for the two or three days preceding the period. The pain was intense during the menstrual period and was worse on the right side and felt "exactly like the old appendix pain." There was a feeling as if something was swelling up in the abdomen. She was very nervous and had some nausea. Beginning just after the period and lasting for about ten days she had diarrhea. On this admission the urine showed many erythrocytes and some albumin. The patient was discharged six weeks after operation as "well."

About three months after her discharge from the hospital some excitement brought about a severe attack of diarrhea, which lasted about ten days. She had had several similar attacks before her third admission to the hospital on March 10, 1913, when a diagnosis was made of "mucous colitis and a possible hyperthryoidism."

Her fourth admission was February 9, 1916, when she was under the care of Dr. Finney and Dr. T. R. Brown. Since August, 1915, her attacks of diarrhea with great rectal pressure and urgency had been increasing in frequency and were accompanied by intense pain in the lower abdomen and over the left sacro-iliac joint. A note was made that there was some tenderness over both groins; the right kidney was

freely palpable, and the tonsils were somewhat enlarged and hard, having been clipped some years previously. At this time the patient had some elevation of temperature and an examination of the blood for malaria was negative. An exploratory laparotomy was done with freeing of adhesions.

In April, 1916, the patient was admitted to the hospital for the fifth time and Dr. Earle operated for a fissure in ano and hemorrhoids.

Dr. Brown continued to treat the patient for her mucous colitis and about two years later she went to Dr. Alfred Riggs of Stockbridge, Mass., who reversed the methods that had been followed in numerous rest-cures, and he gradually got the patient up to a considerable ability for physical exercise, and she was walking twelve to fourteen miles a day before leaving his care.

For about two years she led a fairly normal life, but always had her abdominal pain and whenever she would get her feet wet or get chilled she would have an attack of mucous colitis.

In June, 1918, Dr. Terry Smith of Hartford, Conn., removed her tonsils and adenoids and said they were very bad.

A year later Dr. Brun of Baltimore extacted a tooth and found a large abscess.

In August, 1919, four months before consulting me, the patient was camping on Lake Superior during a week of cold, wet weather and she developed one of her bad attacks of colitis which had persisted. With this she had developed a pressure feeling in the lower left pelvis, which she described as an area of acute pain and pressure about the size of a finger, located in the left groin and extending down through the labium and into the left side of the urethra. This caused a great desire to void and she was often up most of the night. There was a dry feeling in the urethra and vagina and a feeling as if there was a wedge across the pelvis pushing the pelvic bones laterally and interfering with walking. The old rectal pressure, which she had had before her hemorrhoid operation, had returned and when this was bad her mucous colitis seemed to be exaggerated. There was a semi-circular pain reaching from one anterior superior spine region down across the pelvis and up to the opposite anterior spine. When this semi-circular pain became bad there was a pain going through to the sacro-iliac joint region in the left hip, and she felt as if a knot were being tied in this region and causing incapacity of the left leg.

The patient said she could stand most of these discomforts if I could only get rid of the finger-like pressure in the left groin and urethra with the almost unbearable bladder symptoms.

My examination showed that there was some adenoid tissue along the posterior pillars of both tonsils. She still had occasional sore throat and Dr. Smith had promised to burn out this adenoid tissue.

The abdomen was rather long and narrow, the left kidney was not palpable, the right kidney was in second degree prolapse, slightly tender, no desire to void on pressure. Both ureters were tender on palpation at the pelvic brim region with desire to void on pressure. The pelvic organs were absent, the cervix was well up in the vagina and freely movable. The right ureter was extremely tender in the broad ligament region and on pressure over the left ureter broad ligament region the patient said this elicited the finger-like pressure in the left labium and urethral regions. The urine was quite normal.

Since January 2, 1920, I have dilated the left ureter five times, the last time on March 11 with a 5.6 mm. bulb. The right ureter has been dilated three times, the last time on February 27 with a 5 mm. bulb. The patient has a definite stricture in each ureter, the bulb beginning to hang at about 5 cm. above the bladder and hanging through a diffuse area of about 3 cm. length.

Each of these treatments has stirred up all of the patient's previous fantastic symptoms. The treatments have been followed by attacks of diarrhea and mucous colitis with the old rectal pressure, and the treatment on the left side particularly by the old finger pressure in the left groin and urethra and intensification of the bladder symptoms. The old sacro-iliac joint pain with the incapacity of the hip-joint has followed the left side treatments.

I must admit that after taking the patient's history I undertook her treatments with misgivings, and one can readily forgive the patient for entering on a career of new treatments, associated with as much discomfort as belongs to these treatments, with a frank and outspoken skepticism. It has been most gratifying to have her call me up over the 'phone, after the immediate effects of her treatments wore off, and have her say that she was forced to admit that she was getting better.

On her last treatment she said that she had walked about three miles the day before without untoward results. Her mucous colitis had ceased except for two or three days after each treatment. Her bladder improvement began immediately after the first treatments and she is now having very little of the bladder irritation.

Case 6. Mrs. H. L. B., aged fifty years, referred by Dr. H. A. Kelly. The patient had the usual diseases of childhood, no scarlet fever, diphtheria or typhoid. She had pneumonia as a child and again

at fifteen years of age. She had tonsillitis on several occasions with quinsy twice, the last tonsillitis attack five or six years ago. The teeth are in bad condition, showing some extractions, some large fillings, and pronounced pyorrhea. She has had a great deal of trouble with what she calls rheumatism. In the past fifteen years there have been spells lasting two or three days of stiffness of the body and general exhaustion. There is pain in the back and some dull aching and pain in the knees. These attacks are likely to come on every two or three weeks. There have been two attacks of neuritis in both shoulders for which she has been in bed for five or six weeks.

The urinary trouble has been present intermittently for eight years, the attacks coming on about twice a year. Eight years ago she began suddenly with pain in the bladder, frequency, and painful voiding. She entered the local hospital and had daily bladder treatments for five weeks. The trouble continued intermittently from July to October when she had an operation for bad internal hemorrhoids, hoping this would relieve the bladder condition. For about two years she was comfortable and then developing the bladder symptoms again, she had a hysterectomy. Two months following this second operation she began with much pain in the bladder and a weak, sick feeling. She was in the hospital for three weeks on a milk diet, and bladder irrigations with suppositories for the pain

The patient has been in the hospital in the spring and fall of each year, having bladder treatments. Her attacks come on with incontinence which usually occurs while she is out of doors and comes with a gush of urine followed by a leakage which may last fifteen to twenty minutes at at time. She then develops what she calls an "indigestion" pain in the bladder which she may fight off for two or three weeks, when she is struck with a "toothache" pain low in the right side and an intense pain in the urethra.

Dr. Alfred T. Osgood of New York, after a careful investigation in the spring of 1919, operated to tighten the sphincter urethrae muscle. The patient had her usual six months of freedom from symptoms after this operation and when the symptoms again came on in November, 1919, she was sent to Dr. Kelly.

Dr. Kelly found a trigonitis and urethritis but felt that these alone would not account for her symptoms, and he asked me in consultation. From the intermittent character of her bladder symptoms I at once concluded that they were probably due to a focal infection. I considered her "indigestion" pain as probably due to the trigonitis and

urethritis and the sharp "toothache" pain in the lower right side as due to ureteritis.

On examination a pressure by the speculum edge on the trigonum imitated her indigestion pain and the passage of the wax bulb in the right ureter caused her to cry out "there is my toothache pain;" and the hang of the bulb in her stricture area 3 cm. above the ureterovesical orifice caused an uncontrollable desire to void.

This first investigation was made on October 18, 1919, and for three weeks the patient suffered with increased pain. For the first few days after the treatment there was considerable incontinence. She was dilated with a 4.5 mm. bulb on November 21 and then went home for the holidays.

On her return January 27, 1920, she reported a vast improvement in her general health and had no further bladder symptoms except some incontinence in the daytime for the previous three weeks. A 5 mm. bulb was passed on January 7 and a 5.3 mm. bulb on January 21. In the interval six abscessed teeth were extracted.

Her latest reports since going home have been satisfactory but it is too early to draw conclusions in the case of a patient who has been having intervals of comfort lasting six months at a time between her spells of bladder distress. Should she have further trouble in the future we shall have careful investigation of her tonsils because of the bad history with these organs.

Case 7. Mrs. S. F. H., aged forty years—first seen in consultation with Dr. H. A. Kelly at his Sanatorium on December 5, 1919. The patient thinks her first symptoms of bladder trouble came on twelve years ago when there was "a soreness as if in a tube" (the urethra?) and a shivery feeling on voiding. This lasted all one summer and then passed away. About two years later the same symptoms returned and she began to have frequency which increased until six years ago when she began to have a pain in the left labium majus. This is a "sore spot" and a pressure feeling rather than a pain. There seems to be something in the left labium that should not be there, and when the pressure gets bad in the sore spot, she has to void at once. At times she seems to be affected down the left leg and can hardly walk.

She is up ten to twelve times at night and as soon as she voids she goes back to bed and drops to sleep, having no further discomfort until the "sore spot pressure" again awakens her, when she must get up to void immediately. If she attempts to hold the urine there develops considerable distress in the left labium.

Dr. R. R. Huggins of Pittsburgh had treated the bladder intermittently for five years and had recently sent the patient to Dr. John Clark of Philadelphia, who could find no bladder lesion.

Dr. Kelly was unable to find a bladder lesion but with the curious history of the referred pains to the perineal region and down the left leg, he suspected that the patient might have an elusive ulcer of the bladder and asked me in consultation.

In addition to the above history I found on questioning that the patient had had considerable discomfort at times in the past four or five years in the lower left quadrant of the abdomen, just inside the anterior superior spine in the sigmoid region. She said she never had actual pain and that her sore pressure spot in the left labium which caused the bladder distress was not affected materially by automobiling, street car riding or walking. This additional history made me think of the possibility of left ureteral stricture and the improbability of an elusive bladder ulcer because of the lack of actual pain, particularly on exercising.

Cystoscopy gave an entirely negative picture except for a puffy red left ureteral orifice, probably due to a catheterization by Dr. Kelly two days previously.

A wax tipped catheter with wax bulb of 3.6 mm. diameter entered the left ureter with some obstruction to the tip after it was in a few centimeters. On starting the stylet the catheter went on to the kidney, stirring up her old sore spot and desire to void. After some minutes of anuria urine came in normal jets but it was much more bloody than usual with a small wax tipped catheter. On injection to discomfort the pelvis took 9 cc. and returned rapidly 5 cc. This caused the old pain she occasionally had in the sigmoid region.

On withdrawal the small wax bulb hung at 5.5 cm. above the ureter orifice and was difficult to draw through a scar tissue area at this point, and the patient complained bitterly of her old sore spot in the left labium and the desire to void. She said later that she thought I was making extreme pressure on the left labium with my fingers.

She had much of her old discomfort for three days after my treatment and said the old discomfort in the left hip and down the thigh and the weakness in the leg had returned.

She came for a second treatment on March 5, 1920. The bladder distress has been distinctly better. On her best nights she is up once or twice and at her worst is up three or four times as contrasted with the ten or twelve times nightly for the past five years. She has some

of the discomfort at times in the lower left side over the sigmoid region and some of the old sore spot in the left labium which prompts the bladder urgency, but neither of these symptoms were as marked as before her treatment.

Cystoscopy: The urethra dilates without evidence of infiltration. The entire bladder mucosa is normal except for some redness and suggestion of edema about the posterior pole region, which is probably from suction of the obturator on its withdrawal, for the redness fades away during the examination.

Trigonum is normal. Ureteral orifices are normal. The left ureter is catheterized with a wax tipped No. 9 renal catheter with 4.6 mm. wax bulb. The bulb obstructs markedly going in and causes the old sore spot pressure in the left labium.

The kidney is irrigated with silver nitrate solution 1:1000 and takes and returns 7.5 cc. This causes the old pain in the sigmoid region.

On withdrawal the bulb hangs slightly at 11 cm. above the bladder and this does not cause pain. It hangs firmly at 7 cm. above the bladder and through a diffuse area of 3 to 4 cm., causing the old sore spot pressure in the left labium,—"the same pain I have had for years, and this causes the bladder misery."

The limits of time and space prevent the presentation of further case reports. I could have presented many cases in which the bladder distress seems to be permanently relieved after the ureteral treatments, many of these having focal infection areas cleared up before the bladder symptoms improved.

Cases have been chosen rather in which the great difficulties of diagnosis are emphasized, as illustrated by the patients' previous investigations and treatments. I have named the physicians who have had these patients in charge to show that the patients have had the advantages of investigation in the best hospitals, and of medical and surgical care by the best men in our profession. Some of the operations on these patients have been necessary and productive of results, others have just as certainly been unnecessary and without good results.

My operation on case 1 helped her menstrual symptoms and improved her general health but it had no appreciable influence on her bladder symptoms which constituted her chief complaint.

In case 2 we have illustrated the fact that we should never operate the day following a patient's admission to the hospital unless the indications are perfectly clear. In her case a hold-over for study would probably have meant a few treatments for her trigonitis and urethritis, and then the operation for her cystocele and incontinence as the most likely aid to her bladder symptoms. We were not looking for stricture in those days and consequently did not get at the real cause of her symptoms.

I have spoken above of the difficulties of diagnosing stricture as illustrated by the previous treatment these patients have had. As a matter of fact the diagnosis of stricture is not difficult if it is simply borne in mind that this lesion is one of the most common in the abdominal cavity, and that it has fairly characteristic symptoms and signs. The general practitioner and surgeon should be able to make the probable diagnosis from the patient's history and the palpation findings. The urologist may be called to verify or negative the diagnosis by the use of the wax bulb catheter.

With any disease as common as ureteral stricture and having its protean symptoms there may arise many difficulties in differential diagnosis. The urologist can easily learn whether stricture is present, but to decide just what share the stricture has in the patient's complaints may prove a difficult problem. For its solution he may have to call in the gynecologist, the orthopoedist, the neurologist, and a few more specialists; and even then he may have to patiently await the results of his ureteral treatments, combined with the work of the laryngologist, the dentist and the gastro-enterologist before he can draw final conclusions.

AN IMPROVED METHOD OF DETERMINING UREA IN URINE BY MEANS OF UREASE

ANDREW M. ROMAN

From the Hahnemann Medical College and the Columbus Laboratories of Chicago

The discovery of the urease enzyme by Takeuchi (1) established the possibility of a specific test for urea, a fact of which the great army of investigators took advantage and, as a result, published varying methods of so-called quantitative tests for urea in urine.

While every author claimed one or more points of advantage for his method, none of those published up to date measures up to all of the four required points to render a test desirable, viz: first, that it be specific; second, accurate; third, practical, and fourth, give uniform results when performed under the same conditions by different technicians.

This work was undertaken for the purposes of studying all of the current methods, selecting the most satisfactory one and by working over all of its variable factors, finding the cause of errors and correcting the same until the resulting test will conform with all of the above mentioned requirements.

For our study we have selected four methods which are generally accepted and pronounced reliable, viz.:

1. The hypobromite method (2)—using Doremus-Hind's ureometer for the solution, which was prepared by adding 1 cc. of bromine to 30 cc. of 25 per cent sodium hydroxide solution.

2. Gradwohl's modification of Van Slyke's Urease (3) method, fermenting the urine for thirty minutes at 50°C., then aerating the ammonia formed into an acid solution which, after being Nesslerized, is compared on a Duboscq colorimeter against a standard ammonium sulphate solution.

3. Marshall (4) urease method, fermenting the urine with urease for twelve hours at room temperature, after which the

urine is titrated with decinormal hydrochloric acid solution, using a few drops of 0.5 per cent methyl orange solution as indicator.

4. Folin and Denis (5) urease method, fermenting the urine for fifteen minutes at 50°C., adding 1 cc. of metaphosphoric acid solution and 1 gram of blood charcoal; this is filtered and the filtrate Nesslerized directly and compared with a standard ammonium sulphate solution on the Duboscq colorimeter.

This experiment, made on a 2 per cent solution of urea in distilled water and a 0.5 per cent solution of ammonia, shows the erroneous results given by the hypobromite method on ammonia. It should be noted that the readings on the urea solution

TABLE 1

METHOD	2 PER CENT UREA TAKEN					0.5 PER CENT AMMONIA TAKEN				
	Urea per cent found in determination number									
	1	2	3	4	5	1	2	3	4	5
Hypobromite	2.0	2.0	1 9	1 9	2.0	0.4	0.35	0.35	0.45	0.45
Gradwohl-Van Slyke	1.84	1.92	1.92	1.8	1.92	0	0	0	0	0
Marshall	1.65	1.82	1.62	1.90	1.62	0	0	0	0	0
Folin	1.84	1.68	1.68	1.84	1.96	0	0	0	0	0

by the hypobromite method were obtained after four hours standing while the ammonia readings were taken after thirty minutes standing.

Of the current urease methods the Gradwohl-Van Slyke method gave the least variation, both between the individual determination and compared with the known urea content. However, the time and manipulation required for aeration and the probable loss of some urea nitrogen by this process is quite objectionable in clinical determinations.

In performing our experiments we followed the rule of proceeding from the known to the unknown and, consequently, in the foregoing experiments we corroborate still further the findings of other investigators; i.e., the specific action of the urease on urea, the unreliability of the hypobromite method, as well as the impracticability of the present available urease methods.

Decomposition of the peptone by the hypobromite method was completed in three minutes, while with glycocol, uric acid and hippuric acid the reaction was completed in forty minutes.

Since the reaction of hypobromite with urea is not complete within four hours (table 1), it is evident that the urea content of any urine containing appreciable amount of any of these substances could not be determined by this method. It is a proven

TABLE 2

Showing the specific action of urease, in that it does not decompose substances belonging to the amino acid groups, while the hypobromite method, acting upon them, gives grossly erroneous results

METHOD	A 0.5 PER CENT SOLUTION IN WATER OF			
	Glycocol	Uric acid	Hippuric acid	Witte's peptone
	Gave a urea reading of			
	per cent	*per cent*	*per cent*	*per cent*
Hypobromite	0.20	0.16	0.20	0.40
Gradwohl-Van Slyke	None	None	None	None
Marshall	None	None	None	None
Folin	None	None	None	None

TABLE 3

METHOD	NORMAL ACID URINE	PLUS 0.5 PER CENT CREATIN	PLUS 0.5 PER CENT CREATIN AND 0.5 PER CENT UREA
	Per cent of "urea" found		
Hypobromite	2.2	2.2	2.6
Gradwohl-Van Slyke	1.96	2.04	2.48
Marshall	1.78	1.64	2.22
Folin	1.84	1.88	2.32

fact that the hypobromite solution reacts slowly with albumin, a fact which further introduces great errors in the analysis of nephritic urines, if the hypobromite urea action is allowed to go to completion.

A freshly voided normal urine of slight acid reaction was used and three sets of analyses were made at the same time, the first set being the urine alone; second, the same urine plus 0.5

per cent creatin; the third, the same urine plus 0.5 per cent creatin and plus 0.5 per cent urea. The results of this table and of table 4 show that the reaction of the urine and the presence of creatin do not interfere with the action of the urease.

Here, again, the deficiency of the urease methods, except that of Gradwohl-Van Slyke, is apparent.

The results recorded in table 4 were obtained by exactly the same processes as those given in table 3, except that here a pathological urine, of alkaline reaction and containing 1.6 per cent albumin, was used.

TABLE 4

METHOD	PATHOLOGICAL ALKALINE URINE	SAME URINE PLUS 0.05 PER CENT CREATIN	SAME URINE PLUS 0.5 PER CENT CREATIN AND 0.5 PER CENT UREA
	Per cent of "urea" found		
Hypobromite	1.2	1.2	1.65
Gradwohl-Van Slyke	0.84	0.84	1.28
Marshall	0.56	0.66	1.14
Folin	0.72	0.76	1.20

Here, again the deficiency of the Marshall and the Folin methods is pronounced (compared with the Gradwohl-Van Slyke method); whereas the urea value given by the hypobromite method seems wholly unreliable, the high reading being undoubtedly due to action of the hypobromite on the albumin. Here, also, creatin again failed to exert any vitiating influence on any of the methods.

A glance at the table will reveal the widely varying results obtained by these four methods, which we found to be due to one or more of the following factors: improper temperature as well as improper time of fermentation, the dilution of the urine, the amount of Nessler's reagent used, and the process of aeration, which, besides showing an apparently unavoidable loss of some urea nitrogen, proved to be too time-consuming.

Folin's method by direct Nesslerization seemed most practical. However, duplicate tests made on the same urine showed wide

variations; besides, the use of metaphosphoric acid and blood charcoal involve more factors rendering the test too complicated.

Gradwohl's modification of Van Slyke's method, giving the best results, was used as a basis for subsequent experiments. We found that this test would be almost practical if the aeration were omitted. However, the results thus obtained were lower than by the aeration method. Assuming that the low and widely varying readings were due to the imperfect action of the enzyme and cloudiness of the solution, interfering with the reading on the colorimeter, we began working over separately all of the factors which might cause the assumed errors. As shown in table 5 the optimum temperature of the urease is between 38° and 44°C., a fact which proved to be of great value, in that the necessary time of fermentation at this temperature is only twenty minutes, thereby bringing the test nearer the desired standard.

TEMPERATURE COEFFICIENT

The following data were obtained by the method subsequently described on five urea solutions (2 per cent). The data given represent the temperature and the time of fermentation of each experiment.

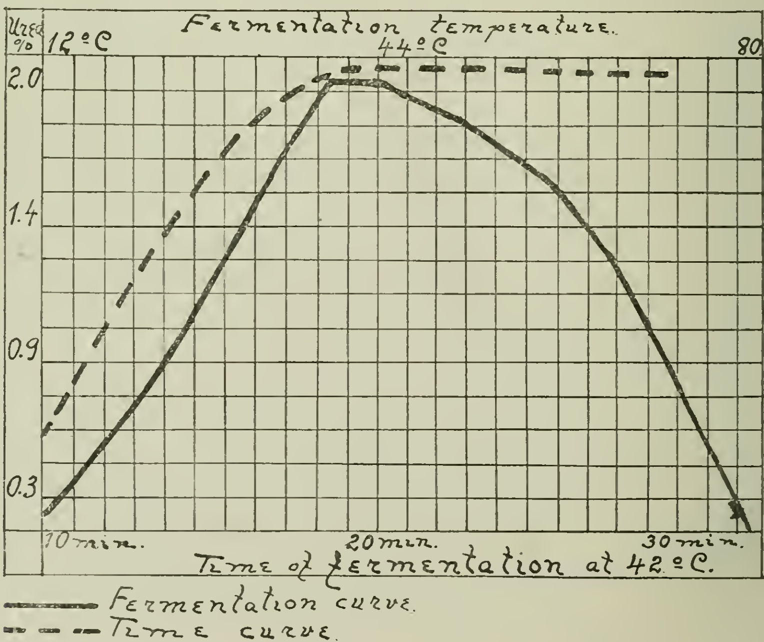
Since 42°C. is the optimum temperature of fermentation and since the action on a 2 per cent solution is complete in twenty minutes, these conditions were adopted for the working clinical method, as the urea content of pathological urines seldom exceeds 2 per cent, the low temperature greatly mitigating the disturbing factor due to the volatility of the ammonium carbonates formed by the reaction.

In searching for some ingredient which might, possibly, interfere with the action of the urease, we failed to corroborate the reported findings of many investigators that creatin, normally present in urine, will retard the action of the enzyme or interfere with the developments of the color after adding Nessler's reagent (6).

We also found that the "reaction" of the urine does not retard the action of the urease, as claimed by Folin (7), as shown in tables 3 and 4.

TABLE 5

TEMPERATURE OF FERMENTATION			TIME OF FERMENTATION		
Determination number	Fermented for 30 minutes at	Urea	Determination number	Minutes fermentation at 42°C.	Urea
	deg. C.	*per cent*			*per cent*
1	10	0.15	1	10	0.60
2	15	0.38	2	12	1.05
3	20	0.70	3	14	1.40
4	25	1.40	4	16	1.72
5	30	1.32	5	18	1.92
6	35	1.70	6	20	2.00
7	40	2.00	7	22	2.00
8	42	2.00	8	24	2.00
9	44	2.00	9	26	2.00
10	46	1.92	10	30	2.00
11	50	1.85			
12	55	1.70			
13	60	1.55			
14	65	1.38			
15	70	1.25			
16	75	0.53			
17	80	0.14			



A sample of urine tested at the same time under the same conditions by five different students gave the following results.

TABLE 6

METHOD	STUDENT NUMBER					MEAN
	1	2	3	4	5	
	Urea per cent on the same urine					
Hypobromite	2.6	2.4	2.4	2.5	2.6	2.50
Gradwohl-Van Slyke	2.30	2.12	2.18	2.24	2.38	2.24
Marshall	1.08	2.24	2.16	1.62	1.84	1.79
Folin	2.12	2.18	1.96	2.06	Lost	2.08

These results are rather instructive from a pedagogical standpoint, but otherwise merely tend to confirm the conclusions already pointed out, best seen in the results given in the last column.

For our experiments on different enzyme preparations we used two freshly prepared extracts, one from the Soya bean, the other from Jack bean meal, as well as a dry preparation placed on the market by the Arlco Products Company.

Not only did the Jack bean extract give the maximum reading of urea (8) as shown in table 7, but it also gave the least cloudiness, and therefore we used it in all of our subsequent experiments. The persistent slight cloudiness was overcome by diluting the urine with nineteen volumes of water and using 2 cc. for Nesslerization, as subsequently described.

The following experiments show that the extract of urease obtained from the Jack bean was more active than that obtained from the Soya bean, or than the commercial sample.

TABLE 7

ENZYME PREPARATION	UREA TAKEN — PER CENT		
	2.0	2.5	3.0
	Urea found — per cent		
Jack bean extract	2.0	2.5	3.0
Soy bean extract	2.0	2.38	2.4
Arlco urease tablet	2.0	2.28	2.4

A preliminary fermentation in an open and in a closed flask showed a loss of ammonia from the open flask of 50 per cent. To avoid the accidental loss of urea nitrogen as ammonia while adding reagents, or due to improper technique, we use a vacuum flask prepared as follows:

A 200 cc. flask is made air tight with a rubber stopper, through which the stem of a separatory funnel passes, the end of which extends one inch below the rubber stopper in the flask. The stop-cock of the separatory funnel is opened and the flask heated at 100°C. in a water bath for ten minutes. Before removing the flask from the water bath, the stop-cock of the separatory funnel is closed. The flask being air tight, a partial vacuum forms in the flask on cooling, which is now ready for use.

As a result of the foregoing experiments and conclusions derived therefrom, we have devised our new method for the quantitative determination of urea in urine.

THE NEW METHOD

Preparation of the enzyme. To 5 grams of permutit (washed by decantation in a 2 per cent acetic acid solution and twice in water), add 20 grams of Jack bean meal and 200 cc. of 30 per cent alcohol. Shake for ten minutes, filter and use 1 cc. of the filtrate for each determination. The enzyme in this filtrate can be kept active for twenty-eight days by adding 0.3 gram of camphor to each 100 cc. of the enzyme solution.

The test.—Dilute the urine to be tested with 19 volumes of water, introduce 2 cc. of the diluted urine into the separatory funnel of the previously prepared vacuum flask and add to it 1 cc. of the Jack bean urease solution.

Open the stop-cock of the separatory funnel just enough to let the urine and urease solution flow into the flask without the entrance of air and close the stop-cock again, thereby mantaining a partial vacuum in the flask. In the same manner 2 cc. of distilled water is added to the solution in the flask for the purpose of washing down any of the enzyme and urine mixture that might have remained in the separatory funnel. The whole

apparatus is placed in an incubator or water bath at 40°C. for twenty minutes.

While fermentation goes on, measure into a graduated cylinder 42 cc. of distilled water and 3 cc. of concentrated Nessler's reagent prepared according to Hawk (9).

When the time for fermentation is up this diluted Nessler's solution is poured into the separatory funnel, and by opening the stop-cock, is added to the fermented urine, with gentle shaking as it flows into the flask so that the Nessler's solution may react with all of the ammonium carbonate formed.

The solution is then immediately compared on the Duboscq colorimeter against the standard ammonium sulphate solution, which is prepared as follows: To 1000 cc. of distilled water add 0.944 gram of ammonium sulphate, this quantity representing 1 mg. of nitrogen in 5 cc. of this solution. In a clean flask place 42 cc. of distilled water, 5 cc. of the standard solution and 3 cc. of Nessler's solution. Place this in the glass container of the colorimeter and set it at 10 on the scale.

The reading. The standard being set at 10, the urine is now matched in color to the standard and the two readings taken. To find the percentage of urea in the urine, divide the reading of the urine into the reading of the standard, then deduct the ammonia nitrogen found by Folin's permutit method (10), and multiply the quotient by 2.14, the result being the urea per cent.

Example. The scale reading of the urine is 14, and that of the standard is 10; 14 divided into 10 equals 0.71—that is, 0.71 mg. of urea nitrogen in 2/20 or 0.1 cc. of urine. This multiplied by 1000 gives milligrams of urea nitrogen in 100 cc. of urine. To convert this into urea, we convert the milligrams into grams and multiply by the factor 2.14, thus:

$$\frac{0.71 \times 1000}{1000} \times 2.14 = 1.51 \text{ grams of urea in 100 cc. of urine} =$$

1.51 per cent urea.

It will thus be seen that the original value, 0.71, represents per cent of urea nitrogen. From this per cent the ammonia nitrogen should be subtracted before multiplying by the urea factor, 2.14.

The numbers in the following table represent the urea in the respective urines, with ammonia correction.

The following tests were performed by this new method by ten different technicians on the same normal and on the same pathological urine at three different times of the same day, showing the reliability of the new method as far as manipulation is concerned.

TABLE 8

NUMBER	9:00 A. M.		12:00 M.		3:00 P. M.	
	Normal urine	Pathological urine	Normal urine	Pathological urine	Normal urine	Pathological urine
1	2.64	1.60	2.60	1.62	2.60	1.62
2	2.66	1.68	2.70	1.68	2.72	1.68
3	2.60	1.60	2.60	1.60	2.60	1.64
4	2.62	1.62	2.62	1.68	2.68	1.62
5	2.62	1.64	2.64	1.64	2.64	1.64
6	2.60	Lost	2.60	1.68	2.64	1.68
7	2.66	1.62	2.66	1.62	2.66	1.60
8	2.62	1.60	2.60	1.60	2.60	1.60
9	2.60	1.60	2.66	1.60	2.66	1.60
10	2.60	1.64	2.60	1.68	2.60	1.68
Means	2.62	1.62	2.63	1.64	2.64	1.64

The following results were obtained on five normal and on five pathological urines by the new method, and are here compared with the results obtained simultaneously by current clinical methods, the Moerner-Sjöquist method being used as the final standard of comparison.

The Moerner-Sjöquist (11) test was performed as follows: 5 cc. of urine are mixed with 5 cc. of saturated solution of barium chloride, containing 5 per cent of barium hydrate; 100 cc. of a mixture of ether and alcohol in the proportion of 1:2 are then added.

After leaving the mixture stand for twenty-four hours, the liquor is filtered off, the precipitate is washed with 50 cc. of the alcohol-ether mixture, the washings are added to the filtrate, and a little magnesia is added. The alcohol and ether are drawn off at a temperature of 55°, and evaporation is continued until the

residue measures 10 to 15 cc. The nitrogen in this is then estimated by the Kjeldahl method; the result, multiplied by 2.143, to equal the amount of the urea.

The numbers in table 9 represent the urea in the respective urines, with ammonia correction.

The normal urines were obtained from the laboratory staff, while pathological urines nos. 1 and 2 were from cases diagnosed as chronic nephritis; nos. 3 and 4 from diabetics, and no. 5 from a case of typhoid fever. The results obtained by the

TABLE 9

METHOD	NORMAL URINE NUMBER					PATHOLOGICAL URINE NUMBER					TIME REQUIRED TO PERFORM TEST
	1	2	3	4	5	1	2	3	4	5	
	Per cent of urea										*hours*
Hypobromite	1.9	1.40	2.25	1.70	2.60	1.25	1.40	1.70	3.00	3.80	4
Gradwohl-Van Slyke	1.68	1.20	2.04	1.36	2.30	0.60	0.92	1.80	2.50	2.82	1¼
Marshall	1.26	0.84	2.00	1.14	1.80	0.46	1.00	1.66	2.10	2.72	12
Folin	1.70	0.90	1.88	1.52	2.00	0.66	0.98	1.60	2.22	2.86	1
Moerner-Sjöquist	1.84	1.20	2.20	1.62	2.56	0.80	1.20	1.80	2.76	3.20 3.20	14
New urease	1.80	1.20	2.22	1.64	2.52	0.80	1.24	1.80	2.76	3.16	25 min.

new method show an almost perfect agreement with the Moerner-Sjöquist method, while the deficiency of the other methods is very pronounced, the three other urease methods showing persistently low results, while the high results given by the hypobromite method on the nephritic urines are again referable to the albumins present.

When the relative time required for the determinations is also considered, the right of the new method to a general try-out seems fully established. The great variations on a mixed diet in the urea content of the normal urines, thus fully established, seems noteworthy.

ACKNOWLEDGMENT

I am very much indebted to Dr. J. C. Blake for suggesting this line of research and for valuable aid as well as generous coöpera-

tion; also to Dr. John A. Wesener and Dr. Adolph A. Gehrmann for valuable aid and supply of material; and to Dr. Regino J. Navarro of the University of the Philippines for information and general aid.

CONCLUSIONS

1. The Jack bean urease enzyme is more active than that of the Soya bean. Its optimum temperature lies between 38°C. and 44°C. for a time of fermentation of twenty minutes.

2. A new method for the quantitative determination of urea in urine by direct Nesslerization is given, which measures up to the four requisite points of pronouncing a test clinically desirable, namely: specific, accurate, practical and giving uniform results when performed by different technicians under the same conditions.

3. An apparatus is used, which essentially is a vacuum flask, by the use of which the escape of ammonia formed is avoided.

REFERENCES

(1) Takeuchi: Jour. College of Agriculture, Tokyo, Japan. Part I, p. 1, 1909.
(2) Todd: Clinical Diagnosis, p. 124, 1918.
(3) Gradwohl-Blaivas: Blood and Urine Chemistry, p. 79, 1917.
(4) Marshall, E. K., Jr.: Jour. Biol. Chem., xiv, 283, 1913.
(5) Folin and Denis: Jour. Biol. Chem., xxvi, 473, 1916.
(6) Folin: Jour. Biol. Chem., xxvi, 497, 1916.
(7) Folin: Laboratory Manual, p. 107, 1919.
(8) Annet, R.: Biochem. Jour. Liverpool, viii, 449, 1917.
(9) Hawk: Physiological Chemistry, p. 329, 1916.
(10) Folin and Bell: Jour. Biol. Chem., xxix, 329, 1917.
(11) Todd, A. H.: Biochem. Jour., xiv, 252, 1920.

THE VALUE OF THE CULTURAL METHOD IN THE DIAGNOSIS OF CHANCROID[1]

OSCAR TEAGUE AND OLIN DEIBERT

From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University

Nearly thirty years have elapsed since the Ducrey bacillus was shown to be the causative agent of chancroids. During the years succeeding its discovery it was found in the pus of a rather large percentage of the chancroids examined and a few strains were readily obtained in pure culture by those workers who required them for their experimental work. However, the discovery of the bacillus has not led as yet to any great practical aid in the diagnosis or treatment of chancroid. This investigation was carried out in the hope of devising a simple cultural procedure for the Ducrey bacillus so that the diagnosis of chancroid could be made in the same way as has become universal for diphtheria. The results obtained have exceeded our expectations.

The Ducrey bacillus occurs in the tissues in long characteristic chains of Gram negative bacilli. As similar chains of non-pathogenic organisms are not found in venereal ulcers, it would seem a simple matter to make a diagnosis of chancroid from smears as is done in gonorrhea. Unfortunately, however, the Ducrey bacilli on passing from the tissue into the purulent discharge of the ulcer lose their characteristic arrangement in long chains and appear as small pleomorphic bacilli, single, in pairs and in groups, and only comparatively rarely in characteristic, though short chains. The presence in smears of pus from a venereal ulcer of small Gram negative bacilli occurring singly or in groups will

[1] This investigation was aided by a grant of funds from the United States Interdepartmental Social Hygiene Board for research in the prevention and cure of venereal diseases.

often furnish considerable evidence of chancroidal infection, but it is probably unsafe to make a definite diagnosis of chancroid without finding the characteristic chains. A study of the literature shows a general agreement that the examination of smears permits of a definite diagnosis of chancroid in only a rather small percentage of cases.

The following quotations may be cited with regard to the value of the diagnosis of chancroid by smears of the purulent discharge:

A smear taken from the surface of the ulcer usually shows numerous pyogenic and other bacteria, and few if any of the pathogenic bacilli. Hence such a smear cannot be depended upon for diagnosis.—Edward L. Keyes, Jr. (1).

In 81 cases, clinically chancroid in which smears were made the Ducrey bacillus was demonstrated 20 times; in 61 smears were negative. —J. E. Moore (2).

An examination of the pus of forty cases of genital ulcerations clinically resembling chancroid was made. In thirty two, bacilli were found corresponding exactly in morphology and staining reaction to the Ducrey bacillus—the characteristic chain arrangement occurring in ten of these.—L. Davis (3).

The Ducrey bacilli occur constantly in the pus of virulent chancroids but their number varies in the pus of different ulcers and even in the pus of the same ulcer on different days. One must often search through many fields of a smear before finding a group of the bacilli and on the other hand several may be found in almost every field. The distribution of the bacilli in a given preparation is usually irregular. In general the virulence of the process and the number of the Ducrey bacilli in the pus run parallel.—Tomasczewski (4).

The secretion from soft chancres is not often examined microscopically for diagnostic purposes. The classical micro-organism which is stated to be found here is Ducrey's bacillus. Generally it is not found, and instead the pus is found to contain large numbers of Gram positive cocci and often clubbed bacilli which are also Gram positive.—L. W. Harrison (5).

The method we have used most successfully for the diagnosis of chancroid by culture is the following one. A rabbit is bled from the heart with a sterile 20 cc. syringe and the blood is dis-

tributed in amounts slightly less than 1 cc. in test tubes about 100 mm. long and 10 mm. in diameter. The blood is allowed to clot at room temperature, is then heated for five minutes at 55°C. and is either used at once or is kept in the ice-box overnight and used on the following day. We found that instead of heating the clotted blood equally good results were obtained when the tubes were simply kept in the ice-box for from three to five days before they were used.

Pieces of stiff iron wire, gauge 18, about $5\frac{1}{2}$ inches long are bent upon themselves at one end for about $\frac{1}{8}$ inch. Ten or twelve of these wires are placed in a 6-inch test tube and are heated in the dry sterilizer. The patient is told to remove the dressing, if he has one, and a bit of the pus from the ulcer is picked up with the bent end of the sterile wire, the latter having been first rubbed gently over the base of the ulcer or under its undermined edge. The pus is then transferred to a tube of clotted blood and is quickly distributed in the serum by passing the wire several times around the clot. A second tube is inoculated in the same way with a fresh wire. After from twenty to twenty-four hours' incubation at 37°C. the serum around the clot is thoroughly stirred with a platinum loop and then a smear is made and stained by Gram's method. Examination with the oil-immersion lens shows characteristic chains of small Gram negative bacilli, sometimes apparently in pure culture, sometimes together with Gram positive cocci or bacilli. If these characteristic chains are present, it is stated that the culture is positive for Ducrey bacilli.

If an antiseptic powder or ointment has been applied to the ulcer, one can usually find a bit of pus that is free from the drug; we have repeatedly obtained positive cultures while the ulcers were under treatment with argyrol, iodoform, ointments or other drugs.

At first we played a stream of sterile salt solution against the surface of the ulcer and then cultured by rubbing the base or edges of the ulcer with the stiff wire. The tubes were inoculated in pairs, most of the material being rubbed off into the serum of the first tube and a new tube being then inoculated with

a smaller amount of material from the same wire. A new sterile wire was used for each new pair of tubes and eight or ten tubes were inoculated from each patient. After a long series of cases had been examined in this way it became apparent that one of the first two tubes was positive practically every time that any of the other tubes showed Ducrey bacilli; consequently, it seemed safe to use only two tubes for diagnosis.

In a further large series of cases we cultured the ulcers in the same media before and after washing them with sterile salt solution and concluded that equally good results with regard to diagnosis were obtained when the time-consuming process of washing was omitted.

As human blood for culture tubes can be readily obtained at venereal clinics when blood is taken for the Wassermann test, we attempted to substitute human blood (heated for different lengths of time) for rabbit blood, but the latter has invariably yielded a better growth of the Ducrey bacillus.

The sterilized iron wires are far more convenient than a platinum loop because they obviate the use of a Bunsen burner or alcohol lamp and can be used in the clinic where the patient is undergoing examination.

This investigation has been concerned with male patients exclusively. We have cultured, in the manner described above, 274 sores[2] occurring on the penis. At most of the clinics we were requested to culture all sores regardless of whether they showed any clinical evidence of chancroid; occasionally, particularly when our supply of culture tubes was running low, we selected the more promising ulcers for culture. Of these 274 sores, 140 yielded cultures that were positive for the Ducrey bacillus, and 134 were negative. In some instances the treatment had been interrupted and a saline dressing applied on the previous day in preparation for the culture, but in the great majority of cases the cultures were prepared either when the patient entered the clinic for the first time often under treatment with some

[2] Many of the patients were cultured repeatedly. We have taken cultures altogether about 350 times.

unknown ointment or powder, or without interrupting the routine treatment of the clinic. We have satisfactory notes on only 69 of the 134 negative cases. These notes indicate that 42 of these 69 negative cases were almost surely patients with primary syphilitic lesions; 8 had erosions or herpes; 8 had sores almost healed; 5 had sores that in all probability were non-venereal and only 6 were recorded at the time of culture as "probably chancroid." Since more than 50 per cent of all the sores cultured by us were positive for the Ducrey bacillus, and since most of the negative cases showed no clinical evidence of chancroid, it follows that a diagnosis of chancroid can be made by means of the cultural method in a very large percentage of the cases—probably above 90 per cent. This result can be obtained without applying any special dressing the day before culturing and, certainly in most instances, without interrupting the usual routine treatment at the clinic.

Through the coöperation of Dr. H. A. Traynor of the United States Marine Hospital Clinic, Barge Office, New York, we were enabled to demonstrate the practicability of the cultural method in a most satisfactory manner. We placed at his disposal some of the sterile wires and culture tubes. He kept the latter in an ice-box, inoculated two tubes from each patient and returned the inoculated tubes to the ice-box. Most of his patients appeared at the clinic in the morning hours and we sent a messenger in the late afternnon to get the inoculated tubes and replace them with fresh culture tubes. Dr. Traynor was requested to culture only ulcers that were clinically chancroid or that he considered double infections of syphilis and chancroid. Of the first 32 cases cultured by him, 22 were positive for the Ducrey bacillus and 10 were negative; i. e., 69 per cent were positive. Later on Dr. Traynor wrote on some of the tubes that a negative report was expected, thus indicating that he was culturing some primary syphilitic sores and our percentage of positives became smaller. In all, 49 cases were cultured by him, and 27 of these were found by us to be positive.

All cultures found by us to be negative after twenty-four hours' incubation were re-examined after forty eight hours' incubation

and consequently reports were not rendered until the end of the latter period. In only a few instances did cultures that were negative at the first examination become positive at the second, and then the first examination had been made after seventeen or eighteen hours instead of twenty. For practical purposes it seems advisable to make a single examination of the cultures and to render a report on the day following the taking of the culture.

The method of culture that we have recommended is not entirely new. Clotted rabbit blood was used by Himmel (6), Fischer (7), Davis (3), and others. They allowed the blood to stand at least two days at room temperature or heated it at 55°C. for thirty minutes. We kept the blood in the ice-box for from three to five days or heated it only five minutes at 55°C. with the idea of retaining a portion of the active complement in order to prevent a too rapid growth of contaminating organisms in the culture. However, we have recently tried parallel tubes of rabbit blood heated for thirty minutes at 55°C. on a few cases and have found that they give excellent results. It is perhaps advisable to use one tube heated five minutes and one tube heated thirty minutes on each case.

The only report of an attempt to employ the cultural method as a routine procedure for the diagnosis of chancroid was made by Moore (2). He cultured 55 cases on blood serum agar and obtained positive cultures only five times. He says: "Obviously, therefore, these methods of microscopic and cultural diagnosis are not to be relied upon." Moore's failure to obtain satisfactory results was probably due to the fact that his culture medium was not a very favorable one for the growth of the Ducrey bacillus.

We have found that great care is necessary to obtain a good growth of the Ducrey bacillus on blood agar plates. The nutrient agar should have a reaction slightly on the alkaline side of absolute neutrality, pH = 7.2 or 7.3; the blood agar must not be too stiff, the surface of the agar must not be dry. It is obvious that the factors favoring the growth of the Ducrey bacillus on the plate will also favor overgrowth of the plate by contaminating organisms. Moreover, the presence of many colonies of con-

taminating organisms seems to inhibit the growth of the Ducrey bacillus to a marked degree. Hence we have used clotted blood exclusively for our primary cultures from the ulcers and have inoculated blood agar plates from the clotted blood tubes after twenty-four hours' incubation in order to obtain pure cultures. We have isolated 70 strains of the Ducrey bacillus in pure culture and all of these are still alive except five that were discarded. The following are the only criteria available at the present time for the routine bacteriological identification of the Ducrey bacillus: (1) It is a small Gram negative bacillus growing in characteristic long chains and tangles in clotted rabbit blood; (2) it forms on blood agar characteristic colonies that readily glide over the surface of the medium; (3) it does not grow on any of the ordinary laboratory culture media with the exception of blood agar.

CONCLUSIONS

It is shown that by a simple cultural procedure the diagnosis of chancroid can be made with almost as much ease and almost as much certainty as the diagnosis of diphtheria by culture.

The methods employed are not entirely new, but it is here demonstrated for the first time that this cultural procedure is a practical method for the diagnosis of chancroid.

The method need not interfere in any way with the usual procedures for the diagnosis of syphilis nor with the treatment of the chancroid.

Note: It is a pleasure to express our indebtedness to the following physicians for having placed at our disposal the material of their clinics: Dr. Stetson, Dr. Clifton, and Dr. Delzell, United States Public Health Service Clinic, Skin and Cancer Hospital; Dr. Kerr and Dr. McTague, United States Immigrant Hospitals, Ellis Island; Dr. Traynor, United States Marine Hospital Clinic, Barge Office; Dr. Parounagian, Bellevue Hospital Clinic; Dr. Rosen, Vanderbilt Clinic, Columbia University; Dr. Foote, Roosevelt Hospital Clinic.

REFERENCES

(1) Keyes, Edward L., Jr.: Urology, 1917, 660.
(2) Moore, J. E.: Jour. Urology, 1920, iv, 169.
(3) Davis, L.: Jour. Med. Res., 1903, iv, 401.
(4) Tomasczewski, E.: Handbuch der Geschlectskranheiten, 1912, ii, 613.
(5) Harrison, L. W.: The Diagnosis and Treatment of Venereal Diseases in General Practice. London, 1918, p. 248.
(6) Himmel, J.: Ann. de l'Inst. Past., 1901, xv, 928.
(7) Fischer, F.: Dermat. Zeitschrift., 1903, Bd. 10, 481.

THE PRECIPITIN REACTION IN THE DIAGNOSIS OF GONOCOCCUS INFECTIONS

G. H. ROBINSON AND P. D. MEADER

From the Department of Bacteriology, School of Hygiene and Public Health, The Johns Hopkins University

The laboratory diagnosis of gonococcus infections is at present accomplished by (1) microscopic examination of pus, (2) the cultivation of the gonococcus from infected discharge or tissue and (3) the complement fixation test upon the blood of the patient.

Microscopic examination is the most extensively used by reason of its simplicity and the rapidity with which results may be obtained. The classical picture is one in which Gram-negative, kidney-shaped diplococci are contained within polymorphonuclear leucocytes. The diagnosis by this method may be readily arrived at in the examination of the urethral discharges in recent infections in the male but becomes more uncertain after the acute stage is passed. In vaginal specimens the abundance of bacterial forms frequently makes a satisfactory report impossible. Organisms resembling the gonococcus in morphology and staining reactions are sometimes found and failure to find the gonococcus is not conclusive evidence that the patient is not harboring this organism. Cultivation of the gonococcus is often difficult owing to the delicacy of the organism. When there is a considerable number of different organisms present as in the case of vaginal specimens, cultural methods are impractical. The complement fixation test seems to be satisfactory in only a small percentage of infections, these being as a general rule in the chronic stage. In view of these difficulties the development of some other method of diagnosis may be of interest.

The work of Krumwiede and Noble (1918) on the diagnosis of pneumococcus infections by the precipitin reaction, that of

Vincent and Bellot (1914) and one of us, Robinson, (1919) on the diagnosis of meningococcus infection by the same method led us to try the value of this reaction in the case of gonorrhea. The literature on the subject is meagre. Watabiki (1918) attempted to diagnose infection by using the serum of the patient with a known gonococcus autolysate. He was able to get a precipitin reaction in a few instances, these being old or chronic cases. No strain specificity was observed. Torrey (1907) has found some strain specificity by using gonococcus autolysates and immune rabbit serum.

In the accomplishment of the precipitin test the preparation of a suitable precipitinogen is of the first importance. Krumwiede boiled pneumonic sputum in a 5 per cent hypochlorite solution. Torrey and Watabiki incubated gonococci in a 0.15 per cent sodium hydroxide solution and then carefully neutralized with acid. Our experience in producing precipitinogen by chemical means showed that the chemical reaction must be very carefully adjusted to the neutral point if false precipitin reactions are to be avoided. We found that if autolysis was permitted in distilled water or preferably in 0.85 per cent sodium chloride solution, a suitable preparation was obtained and in all the work herein reported this method has been used.

It was considered advisable to try the reaction of immune rabbit serum and the autolysate of gonococcus cultures. The cultures included old laboratory strains and others freshly isolated for this work. Animals were injected intravenously with single strains in gradually increasing doses at seven day intervals. Five or six injections sufficed to produce a serum giving a marked precipitin reaction in a dilution of at least one to twenty. The autolysate was prepared by washing off the growth on rabbit blood agar in 5 cc. of physiological salt solution and allowing it to stand in the incubator six hours. This suspension was then centrifuged until the supernatant liquid was perfectly clear. Clear serum was placed in serological test tubes and the clear autolysate stratified over the serum in equal amount, generally 0.25 cc. The tubes were then placed in a water bath at 37°C. for one hour. After the tubes have been cooled either at room

temperature or in the ice-box the results are observed. A positive reaction is indicated by a cloudy white ring at the point of contact of serum and autolysate. The reading of the results is greatly aided by holding the tubes before an electric light. All strains of gonococci gave a positive reaction with immune serum and no differences were noted between the reaction of the homologous and heterologous autolysates so there seemed to be no strain specificity.

The autolysate for diagnostic purposes is obtained by moistening a sterile cotton swab in the suspected material and incubating in two cubic centimeters of physiological salt solution for six hours. The swab is then removed and the infusion is centrifuged until a perfectly clear supernatant liquid is obtained. Occasionally we find that a specimen especially of vaginal origin, remains opalescent in spite of continued centrifugation. We have not as yet been able to overcome this difficulty but the correct reading of the test can be obtained by comparing the density of the precipitated ring in the test tube containing immune rabbit serum with that of the control tube containing normal rabbit serum.

The procedure in brief is as follows: for each specimen to be examined 0.25 cc. of diluted clear serum from two immune and one normal rabbit are placed in serological test tubes. The clear extract of the specimen to be tested is layered over the serum in the same amount. The tubes are incubated for one hour at 37°C. and are allowed to cool before readings are made. Most of the results reported were obtained by the use of serum from rabbits injected with two strains. Two immune sera are used in the test in order to duplicate the results while the serum from a normal animal prevents reading any non-specific precipitation. In the case of some sera there appeared to be a false reaction when sterile salt solution was layered over the serum. This difficulty was overcome by diluting the serum with salt solution and centrifuging until it was perfectly clear. This diluted serum was used in both the test and control tubes in place of the undiluted serum. The dilution used in making the tests is one to two.

When it had been amply demonstrated that pure culture autolysates of gonococci always gave a positive precipitin test specimens of urethral discharge from males having known acute gonococcus infection were obtained. The favorable results from these cases encouraged us to attempt vaginal specimens and others offering a more difficult diagnosis. One hundred and forty-nine specimens have been examined and the results appear to be in accord with the history and clinical examination. The cases from which specimens were obtained fall clinically and by microscopical examination into eight groups. In all but the last group the specimens are from the urinary or genital tract.

Group I. Known positive cases: Those showing Gram-negative, kidney-shaped, intracellular diplococci. The patient gives a history of exposure to infection and the clinical diagnosis is gonorrhea.

Group II. Probably positive cases: The Gram-negative, kidney-shaped diplococci are inconstant or scarce. The history and clinical examination point strongly to infection with M. gonorrhoeae.

Group III. Doubtful cases: The history and clinical examination points to gonococcus infection but microscopical examination reveals no microorganisms or only bacillary forms.

Group IV. Cases under treatment: The clinical diagnosis of each case had been confirmed by microscopic examination of pus. Treatment had progressed so far that no gonococci appeared in the discharge.

Group V. Chronic cases: No treatment had been given for some time. Suspicious organisms are absent from the discharge but clinical symptoms indicate some local infection.

Group VI. Vulvo-vaginitis in children: The microscopic examination showed in each case Gram-negative, kidney-shaped diplococci contained within the leucocytes.

Group VII. Presumably negative cases: Vaginal swabs obtained from women under treatment for conditions other than gonorrhea.

Group VIII. Known negative cases: Pus collected from surgical cases in which the causative agent was known not to be M. gonorrhoeae.

A tabulation of the specimens examined in each group is shown in protocol I.

Group I in which gonococci were present gave positive reactions in each instance. The two cases reported as negative under group II were not positive microscopically. While the history might indicate gonococcus infection there is no proof that this is true. The large percentage of positives in this group, however, indicates a substantial correlation between clinical examination and the precipitin test. The same correlation of results is shown in group III. The results in groups IV and V point to the reliability of the precipitin test as compared with microscopic examination as these cases were microscopically negative. Our one negative result in this group may have indicated a complete cure. Group VI is of interest in view of the findings of Pearce (1915) that the type of gonococcus found in infants was distinct by the complement fixation test from the organism in adult infections. Group VII was made up of patients in a women's medical ward. The case which we found positive was afterward examined microscopically and found to harbor suspicious organisms. The specimens in group VIII comprised pus from a boil, osteomyelitis of the foot, neck abscesses, periostitis of the tibia with a negative Wassermann reaction and an alveolar abscess. In each case a staphylococcus or streptococcus was cultivated.

In order to still further test the accuracy of the precipitin reaction a more complete examination was made of eleven women under treatment for gonorrhea. Specimens were carefully taken from the cervix, urethra and vagina. Protocol II shows the results obtained.

While gonococci were demonstrated in only two of the cases a positive precipitin test was obtained from at least one source from each patient. In four, either the cervix or urethra gave a negative test but the vagina, exposed to infection from either source, was always positive. Where the vagina gave a positive test in the presence of a negative reaction from both cervix and urethra an infection of the vaginal wall itself may be assumed.

It has been recognized by considerable experimental work that the precipitin reaction will detect minute amounts of protein.

The test as applied to the diagnosis of gonorrhea depends upon the presence of the gonococcus protein and should be specific. The gonococcus is notably susceptible to autolysis and it is probable that in the case of a localized infection the products of autolysis might be present in secretions in which the organisms could not be demonstrated.

From these results the precipitin reaction seems to have an advantage over the microscopic examination in three respects, viz.: in testing specimens from cases where the diagnosis is doubtful, in examining specimens containing an abundance of microorganisms such as vaginal secretions and in determining the presence of infection in cases under treatment. The immune serum which we have used, for the most part produced by the use of two strains of gonococci, has seemed to react upon all infecting strains. It is possible that the dilution of serum used is not sufficient to distinguish strain specificity if such a condition does exist. Bacterial species which gave a negative reaction with gonococcus immune serum are M. albus, M. aureus, M. citreus, M. catarrhalis, Strep. hemolyticus, and B. coli. The meningococcus, however, gave a positive reaction when a concentrated pure culture autolysate was used but the gonococcus control autolysate continued to give a positive reaction for a considerable number of dilutions after the reaction with meningococcus autolysate had become negative. It is improbable, moreover, that meningococcus protein would be found in secretions in which the gonococcus was sought.

Work on a large number of cases is in progress to determine the value of the test as a routine measure. The number of cases presumably negative in our series is comparatively small and more are necessary to the establishment of the test on a firm basis. While the number of examinations made in some of the groups reported is not large, sufficient work has been done to warrant certain conclusions.

1. The present methods of diagnosing gonorrhea are inadequate since in many cases, clinically positive gonococci cannot be demonstrated in the discharge.

2. A positive precipitin test is obtained in all cases where the gonococcus can be found in the discharge.

3. A positive precipitin test is found in specimens from many patients whose history and clinical symptoms point to gonorrhea but in whose discharges the gonococcus cannot be demonstrated.

4. The precipitin test is of value in the diagnosis of vaginal and other specimens where the microscopical demonstration of gonococci in the discharge is difficult or impossible.

Material from patients was obtained from the United States Government Clinic, from the wards and dispensary of the Johns Hopkins Hospital, from the Maryland General Hospital and from private cases. Our thanks are due to the physicians and medical students through whose courtesy and assistance the specimens were collected.

Protocol I. Correlation of clinical condition and the precipitin test

GROUP	CLINICAL CLASSIFICATION	M. GONORRHEAE BY MICROSCOPICAL EXAMINATION	SEX	PRECIPITIN TEST		
				Positive	Negative	Total
I	Gonorrhea	Present	Female	19	0	61
			Male	42	0	
II	Probable gonorrhea	Few or inconstant	Female	11	1	22
			Male	9	1	
III	Doubtful	Absent	Female	7	0	10
			Male	2	1	
IV	Gonorrhea under treatment	Disappeared under treatment	Female	9	1	16
			Male	6	0	
V	Chronic gonorrhea treatment suspended	Disappeared under treatment	Female	4	0	6
			Male	2	0	
VI	Vulvo-vaginitis in children	Present	Female	7	0	7
VII	Non—gonorrheal medical cases	Absent except perhaps in one case	Female	1	17	18
VIII	Non—gonorrheal surgical cases	Absent	Not specified	0	9	9
						149

Protocol II. Determination of the location of infection

CASE NUMBER	CERVIX	URETHRA	VAGINA
1	Negative	Negative	Positive
2	Negative	Positive	Positive
3*	Positive	Positive	Positive
4	Negative	Positive	Positive
5	Not tested	Positive	Positive
6*	Positive	Positive	Positive
7	Positive	Negative	Positive
8	Negative	Negative	Positive
9	Positive	Negative	Positive
10	Negative	Negative	Positive
11	Positive	Positive	Positive

* Positive microscopically.

REFERENCES

Torrey, J. C.: J. Med. Research, 1907, xvi, 329.

Vincent and Bellot: Quoted from Besson, A., Technique Microbiologique et Serotherapique, 1914, p. 391.

Pearce, L.: J. Exp. M., 1915, xxi, 289.

Krumwiede, C., and Noble, W. C.: J. Immunol., 1918, iii, 1.

Watabiki, T.: J. Infect. Dis., 1918, xxii, 115.

Robinson, G. H.: N. Y. M. J.. 1919, cix, 464.

TUBERCULOSIS OF THE SPINE RESEMBLING PYELITIS

NELLIS B. FOSTER

Pain due to pressure on spinal nerves resembles that of visceral disease and leads often to extreme difficulty in diagnosis. Since Hilton, of Guy's Hospital, called attention to referred pain, the subject has been of constant interest. Nevertheless unsuspected Potts' disease may be an embarrassing disclosure post mortem.

The varieties of nerve-root symptoms resulting from spondylitis have been described by Marie and Von Becterew especially and in this country there have been several contributions to the literature (McCrae, Vanderhoof). The notable papers by Head are important in explaining the foundation for diagnostic difficulties. Confusion in the diagnosis of disorders has been reported,[1] but the importance of the subject is hardly appreciated generally, and on that account the following case report is of interest; especially so perhaps since the mistake we were endeavoring to avoid actually was made.

It very seldom happens that a lesion of the spine sufficient in extent to cause nerve pressure and therefore pain does not also produce impaired motility; yet occasionally this is the case. Also it may not be possible to induce the typical pain by jar or by posture. Since however the pain is produced by pressure on nerve trunks or roots these nerves are to some extent diseased and therefore there should be and usually is paresthesia, and alterations of sensations in the area supplied by the nerve, and not infrequently disturbances in the reflexes. Trophic or motor changes arise later. Due attention to the neurological manifestations of the spondylitis should prevent the error made in our case.

[1] Chute, Boston Med. & Surg. Jour., 1904, cli, 563; Blaine, Amer. Jour. Roentgenol., 1917, iv, 122.

Attacks of unilateral pain resembling renal colic; intermittent fever and pyuria; cystoscopic examination revealing pus from the kidney on the side with pain; examination of spine and radiograms negative; nephrectomy; later kyphosis and signs of disease of vertebrae.

Patient no. 226602. History. Was admitted November 9, 1919, complaining of dull pain in the lumbar region, sharp shooting pains over the lower sternum on swallowing food, slight cough and bloody urine.

The family history was not significant.

The patient had apparently enjoyed good health during his life time. He had had "intermittent fever" thirty-nine years ago and "acute inflammatory rheumatism" thirty-two years ago, the latter disease confining him to bed for several months. There was no recurrence of the arthritis. He dislocated his right femur fifteen years ago and has had a slight limp since that time. There were no symptoms suggesting involvement of the cardio-respiratory or gastro-intestinal systems. The patient's habits were good, his occupation, that of a clerk, had not been unduly arduous, is a moderate eater and took only beer occasionally.

The present illness began in December, 1918, during a period of hard work at long hours. He gradually lost strength and he thinks he has lost nearly 50 pounds in weight. On the advice of his physician he discontinued work for a couple of months and during this time gained some strength. He felt fairly well until about two weeks before admission to the hospital. He then contracted a hard cold but did not discontinue work. A week ago he noticed that the urine was bloody, there was some burning and increased frequency. Following this there was some puffiness of the face, hands and feet. Eight days before admission had a chill and remained away from his work. Four days ago he resumed work but felt very weak and had some backache. Two days ago there was a stabbing pain in the region of the lower sternum. This pain has persisted, is most marked on swallowing food. Patient does not think he has had fever and has had no headache or vomiting. The appetite has been rather poor.

Physical examination. On examination at the time of admission there was slight fever of 100.2°F. with normal pulse and respiration. Patient was a well nourished man, with the appearance of being acutely ill. The skin was slightly jaundiced. Examination of the eyes, nose,

ears and mouth revealed nothing of significance. There were only a few râles at the bases of both lungs. The heart was normal. Abdomen normal. There was no edema of the extremities, no glandular enlargement and the reflexes were normal.

Pathological course and findings. The urine contained hemoglobin but no red blood cells, and there was considerable albumen. On account of the persistence of the hemoglobin and the absence of other signs the case was investigated for the possibility of paroxysmal hemaglobinurea, but this diagnosis could not be substantiated. Functional renal tests all indicated approximately normal condition. The blood cultures were negative. The course of the disease suggested a low grade infection. The temperature curve averaged between 99° and 100°, with occasional sharp rises to 102° or even 104°, for the period of a day. The urine always showed an increased number of white blood cells and occasional clumps of these. Macroscopic pus was noticed on only two occasions and these times happened to fall on days when there was a sharp rise of temperature. The patient was complaining at intervals of severe pain in the lumbar region and frequently this pain was severe enough to require morphine for sleep. Several radiographic examinations were made without detecting evidence of calculus. Cystoscopic examination showed that there was pus and red blood cells coming from the right ureter while the urine from the left ureter was normal. No tubercle bacilli could be found in any specimens. The bladder appeared normal. A pylogram showed that the right kidney was large.

While it seemed probable that there was an infection of the right kidney the severity of pain suffered by the patient appeared to be disproportionate and on that account a number of examinations of the spine were made and radiographs were done to detect, if possible, evidence of tuberculosis or arthritis of the vertebra. No evidence at all was secured.

After considerable debate, it was determined to remove the right kidney which was done on January 22, 1920. The kidney removed presented some evidence of chronic nephritis with chronic pyelitis, the latter being of a slight degree. Following the operation the patient did remarkably well, the temperature became normal and the pain which had been so persistent, disappeared. The patient was discharged February 6 apparently cured.

Interval note. He did well until the latter part of March when there was a recurrence of the pain in the lumbar region. This dull pain

gradually grew worse and changed to a pain of a stabbing character. During early April the pain began to radiate down both legs to his feet. This pain was now apparently equally severe on both sides. The patient was readmitted to the hospital April 12, 1920.

Physical examination. At this time the notable feature of his examination was a definite angulation involving the 12th dorsal and the 1st lumbar vertebrae. There was tenderness on palpation over this. The patient had a temperature ranging from 100° to 101°F. Radiographic examination indicated a destructive process, quite typical of tuberculosis of the spine.

THE WAX-BULB URETER CATHETER FOR ROUTINE USE

EDWARD L. KEYES, JR.

The application of a wax bulb upon the ureter catheter was first suggested by Dr. Howard Kelly for the detection of ureter calculi, and for use through his open tube cystoscope. It was soon discovered that the bulb could be employed with any type of cystoscope if only the catheter was introduced into the bladder in advance of the instrument and threaded backward into this.

A number of methods have been suggested whereby the wax bulb may be employed through the various models of water distention cystoscopes, such as the protection of the bulb by rubber tubing or by a soluble capsule, all of these devices having the common purpose of protecting the wax from being scratched by contact with the metal instrument, a purpose based upon the fear that a scratch upon the wax made by the instrument might be mistaken for the scratch produced by contact with a stone.

Unfortunately no one of these methods of protecting the wax but adds some complication to the cystoscopy itself; no one of them is, in consequence, applicable to all cases. And yet if the wax bulb is to serve us as it should, it must be employed as a routine procedure, and must not materially interfere with the rapidity or ease of cystoscopy.

Contemplation of this situation leads naturally to the question, Does the cystoscope produce a scratch simulating that produced by a stone? and a few simple experiments immediately showed that it does not. The metal surface of the cystoscopic sheath and lever with which the wax may come in contact are smooth. The imprint made upon the wax by such a surface is a flat one. Urinary calculi, on the other hand, do not have smooth surfaces. They are rough and, as is well known, the imprint left by them upon the wax is a rough one, resembling in miniature the scratch

made by the claws of an animal. Confusion between the two seems, to say the least, improbable. Let anyone with misgivings as to the accuracy of this statement satisfy himself by attaching wax bulbs to his catheters of such a size as to slip freely through the lumen of his cystoscope and so manipulate them as to produce every possible variety of scratch, and compare these with the scratches produced experimentally or in actual practice by urinary calculi.

Once satisfied as to this point, the rest, the application of the method to daily practice, presents no difficulty. It may be detailed as follows:

The bulb. For routine work it is convenient to attach the bulb just back of the third eye of the flute tip catheter. If an olivary tip is used, the bulb may be applied to this. If stone is actually suspected, I first pass a wax-tip olivary bougie, withdraw this, and then proceed to catheterize the ureters with instruments furnished with bulbs at the conventional place.

The size and thickness of the bulbs must vary to accord with the diameter of the catheters employed and the bore of the cystoscope through which they are to be introduced. The bulb must run freely through the cystoscopic channel in which it is to lie. Hence the operator who uses catheters just as large as his cystoscope will carry must reduce the wax to the thinnest possible layer,[1] while he who prefers a smaller catheter in the belief that he thus minimizes the trauma to the ureter, will employ a thicker bulb which will have the advantage of acting as a dam just back of the tip of his catheter to prevent extra-catheter escape of urine into the bladder. Such is the combination favored by me. I find that a no. 5 catheter, introduced very slowly into the ureter, especially for the first 10 cm., passed up until it reaches the kidney pelvis (at least 30 cm.) and then withdrawn a bit, so as to be sure that it is not scratching the kidney parenchyma, produces a minimum of trauma, and therefore results in adequate drainage of the ureter in fully as high a percentage of cases as when a larger instrument is employed.

[1] A bulb large enough to detect ureteral stricture may be affixed to a single catheter in the operating cystoscope.

The bulb should, by the way, always be inspected through a magnifying glass by the operator before it is introduced, so that he may be familiar with the little irregularities upon its surface which, if not inspected beforehand, may prove far more confusing than any scratch produced by the cystoscope possibly could be.

Introduction of the catheter into the cystoscope. The wax-bulb catheter is introduced backward into the telescopic channel, i.e., its butt end is pushed backward through the rubber nipple at the ocular end of the (Wappler type of) cystoscope. Its tendency to catch in the rubber tip is readily overcome by deflecting this a trifle toward the shaft of the telescope as the catheter is being introduced.

The catheter is then threaded into the rubber tip until its vesical extremity lies about half way down the shaft of the instrument.

Introduction of the telescope into its sheath. Some little care is taken to make the catheters lie flat in their grooves as the telescope is introduced into its sheath. If the bulbs are too large they will stick as they are being introduced; if they slip in readily all is well.

Introduction of the catheters into the ureters. The catheters may be introduced into the ureters without any special precautions. They are quite likely to be rubbed by the lever as they pass over it, but this does not greatly matter. If both bladder and patient are tolerant, however, the bulb may be introduced unmarred by the following maneuver: The ureter mouth having been identified, the catheter is introduced until its wax bulb appears in the cystoscopic field. It is then rotated so as to impress its characteristics and any marks derived from the instrument upon the memory of the operator. The lever is now elevated sufficiently to bring the tip of the catheter into the field. If this can be done the catheter is gently introduced into the ureter mouth by manipulation of the cystoscope, the catheter remaining fixed and not elevated or depressed or pushed further upward until it is fully engaged in the ureter.

If, after the catheter has been first pushed into the bladder, elevation of the lever fails to bring its tip back into the field of

vision, the lever must again be lowered, the catheter withdrawn as far as necessary, the lever again elevated, and the catheter introduced into the ureter by a movement of the cystoscope, and the lever again lowered before the catheter is pushed onward up the duct.

This maneuver is the familiar one employed in teaching ureter catheterization to the beginner, with only this one additional precaution, that no motion shall be imparted to the catheter while the lever is elevated.

If a single catheterizing instrument is employed, the wax bulb may be employed for both sides by keeping the cystoscope in place while the first ureter is being catheterized, withdrawing the catheter, inspecting its bulb for scratches, and then introducing it into the second ureter, all without withdrawing the cystoscope from the urethra.

Withdrawal of the catheter. As a rule the catheters are withdrawn in the usual manner, after the withdrawal of the cystoscope. If special maneuvers are employed, such as the preliminary introduction of a wax tipped bougie, scratches upon this may be fully identified by inspection under the magnification afforded by lens of the cystoscope (subsequent routine inspection with the magnifying glass will verify these), or catheter and telescope may be withdrawn in one piece without any risk of scratching by the sheath, so long as the precaution is taken to keep the window of the cystoscope well within the bladder, so that the catheter shall not be pressed against the sheath by the urethral wall.

I have employed this routine method of using wax bulb ureter catheters for more than a year in my office practice, and it has been used by my associate, Dr. Herbert Mohan, in my service at St. Vincent's Hospital during this same period. Neither of us has had the least difficulty in differentiating instrumental scratches from stone scratches. The procedure has once disclosed an unsuspected ureter stone.

My firm belief that many ureter stones are not discovered simply because they are unsuspected and are not disclosed by X-ray, impels me to urge the general employment of the routine use of the wax bulb as described above.

SOLITARY CYSTS OF THE KIDNEY[1]

HERMAN L. KRETSCHMER

Chicago

Large solitary and multiple cysts of the kidney are rare, and as evidence of this statement the following data are presented:

1. The literature dealing with this condition is not large and case reports are few and far between. To illustrate: In 1906 Simon was able to find but 52 cases reported in the literature. Isolated cases have been reported since then—47 according to my knowledge, and with the case reported here the number, since Simon made his report, is 48.

2. This condition is infrequently met with during operations upon the kidney. Israel found it only once in 297 surgical conditions of the kidneys. Cunningham, who presented a paper on this subject before this Association in 1916, reported 4 cases upon which he had operated.

3. Autopsy statistics also prove that it is a rare finding in the postmortem room. According to Morris, 5 cases were found in 2610 autopsies at the Middlesex Hospital, London. Eleven of the 47 cases reviewed in this paper were found at autopsy.

Congenital polycystic disease and the small cysts met with in chronic nephritis are not to be confused with the large solitary cysts, as has been done by some authors. These lesions will not be considered in the discussion at this time.

Because of the infrequent occurrence of solitary cysts of the kidney, the following case is not without interest.

W. K., male, aged fifty-seven. Referred by Dr. Don Abbott.

Previous illnesses. Typhoid fever and scarlet fever many years ago; an attack of rheumatism eight or ten years ago; three attacks of gonor-

[1] Read at the annual meeting of the American Association of Genito-Urinary Surgeons, May 31, June 1–2, 1920, at Rochester, Minnesota.

rhea in his twenties (no complications); evidently made a complete recovery from these attacks. Operation for removal of part of the uvula at twenty-six.

Present illness. Four months ago, at which time he was stretching and rubbing his abdomen, patient felt a mass in the lower right quadrant which seemed to be inside the abdomen; tenderness and pain absent. Mass was hard and could be moved around without pain and could always be felt. Mass has somewhat increased in size since first being noticed. Previously, patient had noted nothing wrong. Also complained of a slight ache in the lumbar region, which has been present on and off for years.

Bowel distress. For the past several months patient has had some bowel distress, complaining chiefly of the presence of gas in the bowels and of some constipation.

Prior to the accidental discovery of the mass, patient had been in good health without ache or pain. For two or three years it had been necessary to void once or twice at night. However, this symptom had not been very marked and had given him but little concern. No increased frequency during the day.

Family history. Father died of kidney trouble at seventy-one; nature of the kidney trouble unknown to patient. Mother died of dropsy when young. One brother living and well. Wife and two children living and well; no history of miscarriage.

Physical examination (Dr. Don Abbott). A slightly plethoric, middle-aged white male, appearing and feeling well. Scalp, nose and ears: negative. Left pupil: sluggish reaction to light; right pupil: larger than left and regular in outline; good reaction to light. Uvula—scars and puckering. Teeth: many fillings and some pyorrhea. Tonsils: moderate in size and boggy. No râles in lungs. Heart: aortic second greater than pulmonic second. Spleen and left kidney: not palpable. Liver: sharp and indurated; not tender. In the right lower quadrant of abdomen a hard, smooth and only slightly irregular mass which moved with inspiration and expiration; not tender; firm in consistence; readily movable. Reflexes lively.

Rectal examination (H. L. Kretschmer). Prostate symmetrical, smooth and slightly increased in size.

Examination of blood. Erythrocytes 4,240,000; leucocytes 9,000; hemoglobin 77 per cent. Blood pressure: systolic 225; diastolic 130. Wassermann reaction negative.

Roentgen-ray examination (fig. 1). Left kidney outline visualized and extends down to the level of the upper margin of the third lumbar vertebra. Psoas muscle outline on left side visible in its entirety. On the right side is seen a large, rounded area of the same general density as the kidney outline on the left side, which extends downward

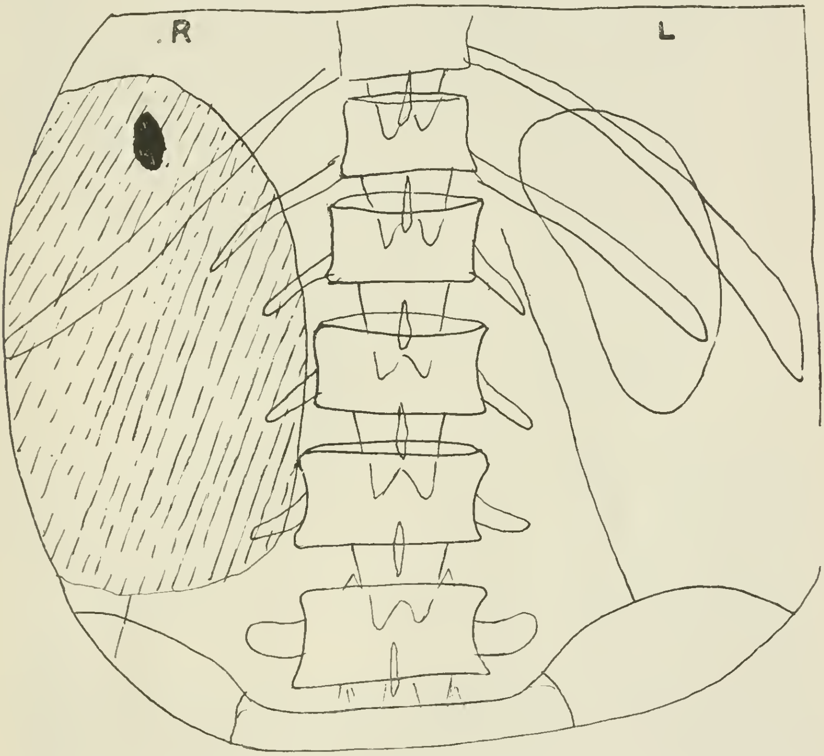


Fig. 1. Tracing of the First Roentgenogram Showing Left Kidney Outline of the Large Cyst and Presence of a Calculus

to the upper border of the fourth lumbar vertebra, just beyond the spinal margin mesially, and to the outer border of the plate. The transverse processes of the spine on the right side are not easily visible, being covered by the presence of the above-mentioned shadow. A small amount of psoas muscle visible just below this shadow and above the crest of the ilium.

In the upper part of this shadow is a shadow that corresponds in its location to a calculus in the renal pelvis. A second plate made in the region of this shadow shows a more distinct shadow located between the eleventh and twelfth ribs, which was diagnosed as a renal calculus.

Cystoscopic examination. There was some difficulty in introducing the cystoscope because of an obstruction in the prostatic urethra. Internal urethral orifice irregular in outline, especially on the right side, showing a small amount of prostatic tissue protruding into the field. Trigonum fluffy; generalized trabeculation; ureters reached with difficulty because of the prostatic enlargement; ureters catheterized without difficulty or obstruction. Examination of urine obtained by ureteral catheterization showed the following:

RIGHT KIDNEY	LEFT KIDNEY
Clear Acid Few leucocytes Cultures sterile	Clear Acid No leucocytes Cultures sterile

Pyelogram. Forty cubic centimeters of a 15 per cent solution of thorium nitrate were used. This showed the pelvis of the right kidney to be situated opposite the second lumbar vertebra; pelvis somewhat enlarged. Above and overlapping the pelvis was a large, irregularly shaped cavity, the shadow of which was more dense than the rest of the pyelogram, indicating the presence of a larger volume of thorium solution. This cavity extended from the eleventh rib, near its upper margin, to below the twelfth rib. It was in this position that the shadow of the calculus was shown. The outline of the ureter could be seen running across the bodies of the second and third lumbar vertebræ, being displaced mesially by the large cyst.

Operation (December 2, 1919). Under general anesthesia an incision was made in the right lumbar region, cutting skin, fascia and muscles. After bluntly pushing away the retroperitoneal fat, a mass with a smooth surface came into view, ovoid in shape. This mass was found to be attached to the lower pole of the right kidney. Attempts to deliver the kidney and the large mass in toto failed, because of the short distance between the lower costal margin and crest of the ilium, and also because of the enormous size of the cyst. In the attempt to deliver the kidney and large cyst, the latter broke, and this was accom-

Fig. 2. Pyelogram Showing a Dilatation of the Upper Half of the Pelvis

panied by the escape of a *brownish fluid* together with *old blood clots.* The cyst was about three or four times the size of the kidney. A second cyst, about 1 inch in diameter, was seen in close proximity to the large cyst. Three smaller cysts were seen in the lower half of the kidney (fig. 3). A stone could be felt in the renal pelvis.

Fig. 3. Showing the Large Cyst Springing from the Lower Pole of the Right Kidney and the Presence of Four Smaller Cysts

It was decided to resect the large and small cysts. During dissection, one of the larger blood vessels was injured, so that a rather sharp hemorrhage occurred. It was then decided to perform a nephrectomy. Two kidney clamps were placed upon the pedicle and the stump ligated distal to the clamps after the kidney was removed. Iodoform gauze was packed about the clamps and the wound closed by suturing the muscles with catgut and the skin with silk. Clamps removed at the end of fifty-four hours.

Postoperative course. 1. Hiccough. On the fifth day after operation, the patient developed hiccough, very severe and distressing, lasting for three days.

2. Following the hiccough, patient was very much confused, confusion lasting for a few days.

3. Following the operation there was a marked decrease in patient's blood pressure. The following readings were obtained:

December 29, 1919: Systolic, 160; diastolic, 90.

February 26, 1919: Systolic, 190; diastolic, 110.

April 10, 1920: Systolic, 170; diastolic, 100.

Urinalysis (after operation). Pale amber in color; acid; trace of albumin; sugar and blood negative. Many amorphous urates. *Urinalysis* (just before leaving hospital). Straw-like in color; acid; specific gravity, 1020; albumin, blood and sugar negative. A few epithelial cells; a few leucocytes and amorphous urates.

Gross description. Specimen is a kidney with about the normal weight of renal tissue; rather elongated and narrow. To the lower pole is attached a smooth spherical mass about three or four times the size of the kidney, brown in color. There are three other fluid-containing masses, the largest of these not over 6 cm. in diameter. *These cysts contain a clear, yellow fluid, but the largest one is full of flocculi,* a lot of fibrin and blood pigment. On opening the kidney, a double pelvis is seen, each separated by renal tissue. In the superior pelvis, lying in a pocket behind, is a black cockle-bur stone about 1.5 cm. in diameter. The cortex of the kidney is about 6 cm. in diameter.

Histological examination. Some of the glomeruli showed an increase in the nuclei of the malpighian tuft. In others there was a marked thickening of Bowman's capsule. Here and there were glomeruli in which the malpighian tuft had been replaced almost entirely by fibrous tissue.

There were many areas of round cell infiltration in practically all of the sections examined. Some sections showed an increase in the interstitial connective tissue.

The cyst wall was made up of fibrous connective tissue, no lining cells being seen. The adjacent kidney tissue appeared to have undergone a slight amount of pressure atrophy.

DISCUSSION

A diagnosis of beginning hypertrophy of the prostate was made from the cystoscopic examination.

From the physical examination it was believed that the large mass in the abdomen had its origin in the right kidney. The mass was evidently attached to the kidney; it moved with respiration; and when one hand was placed on the loin and one hand over the tumor, a sense of ballottement was obtained.

The roentgen-ray examination showed a shadow, which from its shape and position was interpreted as a stone in the renal pelvis, hence the diagnosis of nephrolithiasis. A round shadow was also evident, which in its contour and position corresponded to the large tumor mass that could be demonstrated by palpation (fig. 1).

One point that remained in doubt was the nature of the tumor. Because of the patient's age, the size of the tumor mass, the absence of subjective symptoms, the presence of enlargement on one side only, and also because of the frequency of a tumor at the patient's age, a provisional diagnosis of tumor (probably hypernephroma) was made. *But the pyelogram was not that usually seen in tumor.*

In the differentiation, the only other kidney condition considered was the possibility of a hydronephrosis. The points that lent color to this view were the following: the smooth surface of the tumor and the fact that ballottement could be elicited rather seemed to favor a tumor containing fluid. But the pyelogram did not correspond to that seen in large hydronephroses.

It was difficult to explain the presence of so large a hypernephroma without its being more or less fixed, and this tumor, as stated above, was freely movable. Likewise it was difficult to understand why so large a hypernephroma should not have produced more systemic disturbances, such as loss of weight,

anemia, or possible evidence of metastases. A polycystic kidney was excluded because of the unilateral lesion and solitary cyst because of its extreme rarity.

A casual review of similar cases in the literature shows that error in diagnosis is not uncommon in solitary cyst of the kidney. The cases in which a preoperative diagnosis was made are very few. Thus, Haenisch made a positive diagnosis of cyst of the kidney, his diagnosis being based on the roentgen-ray findings. Bockenheimer, in his case, made a preoperative diagnosis of benign cystic tumor. His patient was a boy eight years old, admitted to the hospital with a tumor of the kidney as shown by the roentgen-ray, and the examination left no doubt as to the nature of the tumor (benign cystic), since there was distinct fluctuation. These two cases are the only ones that I have found in which positive roentgen-ray findings are recorded and in which a correct preoperative diagnosis was made.

Le Fur made a preoperative diagnosis of blood cyst of traumatic origin and this was verified by operation. In both of Wulff's cases the roentgen-ray findings were negative.

Solitary renal cysts have very frequently been mistaken for lesions of other abdominal viscera. In quite a few instances the pathology was correctly associated with the kidney, although a correct pathological diagnosis was not made, as in the case reported in this paper. The following preoperative diagnoses were made: Tumor or unilateral hemorrhagic nephritis (Wulff); tumor (Wulff); hydronephrosis and ptosis (Maguini); intermittent hydronephrosis (Vogel); movable kidney with tumor (Fowler); hypernephroma (Schulman); tumor (Guilini); rupture of kidney (Lipskeroff); stone in kidney (Cunningham).

Cassioli made a preoperative diagnosis of ovarian cyst, hydatid of liver, or suppuration of kidney, and Chiasserini, ecchinococcus or hydronephrosis.

Not infrequently the condition has been confused with large ovarian cysts; a frequent error in diagnosis that has been reported. In 5 of the 47 cases reviewed, a diagnosis of ovarian cyst was made, as recorded by Engländer, Blanchard, Purslow, Boldt, Sarkissiantz and Cunningham.

A preoperative diagnosis of a lesion of the gall-bladder was made by Cunningham, Vogel and Lund.

In several instances the lesion was diagnosed as renal with no record in the reports of just what type of lesion was suspected before operation, and in a large number no preoperative diagnosis was made.

Among the rare intra-abdominal lesions diagnosed, we find intraperitoneal cysts (Paus) and mesenteric cyst (Bevers). Enlargements of the spleen and tuberculous peritonitis have been mistaken for large cysts of the kidney. When the tumor on account of its size, interferes with the action of the bowels, symptoms of intestinal obstruction may be present.

ETIOLOGY

As regards the etiology of this condition, nothing definite is known. Reference to the various theories will be made in passing, but a discussion of these theories will not be entered into in detail, since this was in a thorough manner done by Caulk in his paper, read before this Association a few years ago.

In a discussion of these cases a tendency is evident to include the small multiple cysts of the kidney, which are seen in lesions such as chronic interstitial nephritis, arteriosclerotic kidney, etc., but a line of demarcation should be drawn between these lesions and the large solitary and multiple cysts under consideration in this paper.

As to the formation of these cysts, a congenital theory has been advanced by a large number of authors, while others see a relationship in the etiology between them and the polycystic kidney. Caulk says: "Those who contend that all kidney cysts are of congenital origin are unquestionably making a statement which is unjustifiable."

Many authors have advocated the so-called retention theory, believing that the cysts are due to retention and that this retention is due to an obstruction. Caulk is of the opinion that the majority apparently belong to the class of retention cysts, following obstruction.

Cunningham states that the large, solitary, serous cysts producing abdominal symptoms are very uncommon and are probably due to some undiscoverable obstruction in the uriniferous tubules and the continued excretion of urine. He also states that they are generally unilateral and are considered large retention cysts by those who have studied the subject.

SYMPTOMS

Because there is no symptom or symptom-complex characteristic of solitary cysts, the infrequency of a preoperative diagnosis can readily be understood. Among other reasons are—

1. The rarity of the condition, hence the possibility of its presence not being considered in the differential diagnosis.

2. The fact that by far the largest number of cases reported in the literature were noted before the advent of our present accurate methods of urological diagnosis.

Age. Solitary cysts of the kidney occur most frequently after thirty, being a disease of adult life. Very few cases have been recorded before thirty, although isolated cases have been reported in very young children. Albarran and Imbert state that the youngest case in their series was sixteen months old. In Zaccarini's case the age was mentioned as three years and in Beneke's case, four and a half years. In the cases embraced in this paper, the following age notation was found:

	Cases
1 to 10 years	3
11 to 20 years	1
21 to 30 years	2
31 to 40 years	10
41 to 50 years	3
51 to 60 years	10
61 to 70 years	10
71 to 80 years	3
Age not stated	6
Total	48

It will be seen that of the 42 cases in which the age was stated 36 occurred after the age of thirty.

Sex. It has frequently been stated that solitary cysts of the kidney occur more often in the female than in the male. Brackel, in a series of 21 cases, found that the disease occurred 14 times in females. Albarran and Imbert, on the other hand, noted its occurrence 13 times in males and 10 times in females in cases studied since 1890 In this series the conclusions reached were females 22, males 20, sex being unknown in 6 cases. Judging by these statistics the conclusion to be drawn is that the disparity between the sexes is negligible.

Tumor. The presence of an abdominal tumor is the first thing that attracts the patient's attention, premonitory symptoms being often lacking. The enlargement is not always a frankly marked tumor according to Paus, who has reported a "heavy feeling," Beneke and Boldt "increase in the size of abdomen," Brockenheimer "fullness and pressure," Cassioli "enlargement of the abdomen," Cunningham "swelling in the region of the gall-bladder." Despite these observations, definite tumor formation has been noted in a large number of cases. In the case reported in this paper the patient's chief complaint was the presence of a tumor mass which he discovered quite accidentally while stretching. Moreover, Maguini, Engländer, Blanchard and others have noted the presence of a tumor. In 28 cases the presence of a tumor, swelling or enlargement was revealed by palpation.

Hematuria. Gross blood in the urine is not a frequent occurrence. According to Wulff's case reports it occurred in 2 cases, in Guiliani's in 2 cases, and it has been reported by Le Fur, Katzenberg, Malherbe, Lipskeroff, Caulk and Cunningham. In Lipskeroff's case the bleeding may have been due to the trauma for which the patient was operated upon, and not to the cyst which was found at the time of operation.

Pain. Pain has been variously described as a dragging pain, heaving pain, pain in the lumbar region and pain that was constant. In some cases pain was described as colicky—the pain of renal colic. The characteristics were those of pain often associated with the more common surgical lesions of the kidney.

Gastrointestinal symptoms. The patient reported in this paper complained of some slight intestinal distress for three or four months before he discovered the tumor or consulted a physician. His complaint was chiefly in regard to gas in the bowels and to some constipation. It would be well to emphasize here that when the tumor reaches an enormous size, its presence may interfere with the action of the bowels and lead to a predominance of bowel symptoms. In Bever's case a great deal of constipation was noted.

Pyelograms. On account of the fact that many reports of solitary cyst of the kidney date back a number of years, before the advent of pyelography, the records show pyelograms only in 1 case, namely Schulman's, who made a diagnosis of hypernephroma after pyelography. In recent times Braasch, in his book on pyelography, shows pyelograms of this disease, but these do not correspond with the pyelogram obtained in this case, due entirely to the difference between Braasch's case and the case reported in this paper. In the case reported here, in addition to the solitary cyst, there was a bifid pelvis and a large stone, the latter having produced enlargement of the upper pelvis.

Associated pathology. The case reported here was characterized by a large solitary cyst and multiple cysts (four in number) and also by a double or bifid pelvis. At operation a single calculus was found in the upper pelvis which was hydronephrotic. Both the calculus and hydronephrotic pelvis was demonstrated roentgenologically prior to the operation. The only case similar to the one reported here, which I have been able to find in the literature, is that recorded by Henry Morris in his book on "Surgical Disease of the Kidneys," with this difference, that his case did not show any changes in the pelvis. Vogel reported a case in which a stone was found in the pelvis, and in one of Cunningham's cases a stone was demonstrated by means of the roentgen-ray. In 2 cases reported, in addition to the cyst, renal tuberculosis was present. In Desnos' case the tuberculosis was found in the upper pole. Sarkissiantz found tuberculosis of the kidney associated with amyloid degeneration and arteriosclerotic changes.

Among other rare associated pathological conditions may be mentioned horse-shoe kidney (Brockenheimer), hypernephroma (Cunningham), and anomalies of the renal blood vessels (Fowler).

DISTRIBUTION

Solitary cyst of the kidney is a unilateral disease, and this is one of the distinguishing points used in differentiating it from polycystic disease, generally admitted to be always bilateral. Simon who reviewed the literature and reported 52 cases in 1906, the largest number of cases collected by any one author that I have been able to find, likewise states that it is a unilateral disease. In this series I was able to find only 2 cases in which the disease was present on both sides and these were reported by Zaccarini and Cunningham. The cysts were found at autopsy. One of the patients was three years of age and was operated upon for irreducible inguinal hernia. The direct cause of death was hypertrophy of the thymus

In the remaining cases only one kidney was involved, the cysts being found in the right kidney 21 times, in the left 20 times, and no mention of which kidney 5 times.

SIZE OF CYSTS

The size of the cysts is variable, expressions such as the size of hazelnuts and walnuts, a child's head, double fist, and large, appearing in the literature. More exact terms have been used: seven months' pregnancy (Boldt) and measurements, 4 litres (Le Fur). The largest cyst was reported by Cassioli who stated that his patient's cyst contained 12 litres.

LOCATION

In 11 cases the cyst was located in the upper pole and in 13 cases in the lower pole. In Fowler's case the cyst occupied part of the lower third and part of the middle third: in Paus' it was situated on the anterior surface, and in Vogel's in the middle of the anterior surface In Le Fur's case the cyst originated

on the anterior surface and in Sarkissiantz's it sprang from the outer border, while in one of Cunningham's cases the cyst was described as springing from the lower pole and hilum.

CONTENTS

In a large number of cases the character of the contents was not stated. In the majority of cases in which mention of the contents was made, the contents were described as clear serous fluid. Bloody fluid or clots occurred in few cases. In one of Wulff's cases the character of the fluid is described as thin fluid and blood, and as bloody in the other case Giuliani stated that clots were found in his case and in Recamier's case the contents were serosanguineous. In Lipskeroff's case the contents were bloody, but this was probably due to the trauma.

In the case reported in this paper the large cyst contained old clotted blood and the smaller cysts, clear straw-colored fluid.

TREATMENT

It is universally agreed that the logical treatment is resection of the cyst, provided that this can be carried out; this is feasible if there has not been too much destruction of kidney tissue.

Nephrectomy must sometimes be resorted to when complications arise during the course of the operation, such as uncontrollable hemorrhage In 16 of the 48 cases included in this paper, nephrectomy was carried out, and in 18 either excision or resection. Eleven were found at autopsy, and in 1 no mention was made of the type of operation. In 1 the sac was sutured to the abdominal wound.

Of the 35 patients that were operated upon, 2 died. In one death was due to bronchopneumonia, in the other, erysipelas. One patient died of peritonitis, but this was probably the result of many tappings. One patient died following an operation for inguinal hernia, death being due to hypertrophy of the thymus. In this case the solitary cyst was found at autopsy.

SUMMARY

1. Solitary cysts of the kidney are rare.
2. They occur with about equal frequency on the right and left sides.
3. The sexes appear to be about equally affected.
4. The cysts usually originate from one pole, either upper or lower.
5. The disease is not commonly met with in the first two decades of life.

REFERENCES

Abell, I.: Urol. and Cut. Rev., 1916, xx, 617.
Engländer, B.: Arch. klin. chir., 1902, lxv, 112.
Paus, N.: Deutsch. Ztschr. f. chir., 1915, cxxxii, 197.
Rendu: Ann. de gynéc. et d'obst., 1898, p. 159.
Blanchard: Rev. de Chir., 1913, xlvii, 913.
Wulff, O.: Arch. f. klin. chir., 1915, cvi, 689.
Zaccarini: Deutsch Ztschr. f. chir., 1915, cxxxii, 295.
Maguini, M.: Policlinico, 1917, xxiv, 180.
Beneke: Centralbl. f. allg. path. Anat., 1910, xxi, 996.
Bevers, E. C.: Brit. Med. Jour., 1914, i, 702.
Purslow: Brit. Med. Jour., 1913, i, 884.
Recamier: Ann. d. mal. d. org. gén.-urin., 1893, xi, 185.
Pasquereau: Rev. d. Chir., 1913, xlvii, 775.
Roche, F.: Ann. d. mal. d. org. gén.-urin., 1898, xvi, 1139.
Vogel, R.: Zentralbl. f. Chir., 1912, xxxix, 2, 1540.
Fowler, Russel S.: N. Y. Med Jour., 1911, xciv, 1109–1111.
Schuman, Maximilian: N. Y. Med. Jour., 1916, civ, 218–219.
Boldt, F. J.: Am. Jour. Obst., 1906, liv, 864.
Thompson, H.: Pr. Path. Soc., Lond., 1861–1862, xiii, 128.
Desnos: Ann. d. mal. d. org. gén.-urin., 1911, xxix, 1989.
Le Fur: Ann. d. mal. d. org. gén.-urin., 1911, xxix.
Guiliani: Lyon. Med., 1913, cxxi, 109.
Bockenheimer, P.: Berl. klin. Wchschr., 1911, xlviii, 2, 1641.
Malherbe: Ann. d. mal. d. org. gén.-urin., 1890, viii, 268.
Haenisch, L. F.: Fortschr. a. d. Gebiet. d. Rontgenstrahl., 1910, xv, 300.
Lipskeroff, A.: Fol. Urol., 1912, vi, 375.
Cassioli, C.: Rivista Ospedal, Roma, 1917, vii, 151.
Simon, J.: Thèse, Paris, 1906.
Chiasserini, A.: Clin. Chir., Milano, 1916, xxiv, 964.
Sarkissiantz, A.: Arch. mens. d'obst. et gynec., 1913, iv, 341.
Przewoski: Gaz. Lekarska, xxiv, 820.
Hoffman, K.: Inag., Dissert., Königsberg, 1895.
Obalinski: Wien. klin. Wchschr., 1891, iv, 719.

Albarran and Imbert: Tumors of the Kidney, 1905, p. 501.
Tuffier: Arch. gén. d. méd., 1891, July 10.
Tuffier: Arch. gén. d. méd., 1891, ii, 5.
Hildebrandt: Deutsch Ztschr. f. Chir., 1894, xl, 99.
Morton, Chas. A.: Lancet, London, 1908, ii, 520–521.
Delkeskamp: Beitr. z. klin. Chir., 1904, xliv, 58.
Dominici, L.: Fol. Urol., 1910, v, 151.
Karo, W.: Deutsch. med. Wchschr., 1916, xlii, 2, 1320.
Ruckert, A.: Path. anat. Arbeit., Joh. Orth. Jubil., 1903, 475.
Morris, H.: Surgical Diseases of the Kidney and Ureter.

INDEX